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Italian Guidelines for the Use of Antiretroviral Agents and the Diagnostic-clinical Management of HIV-1 Infected Persons

Andrea Antinori[1], Simone Marcotullio[2] Adriana Ammassari[1], Massimo Andreoni[3], Gioacchino Angarano[4], Giampiero Carosi[5], Paola Cinque[6], Antonella d'Arminio Monforte[7], Giovanni Di Perri[8], Barbara Ensoli[9], Enrico Ferrazzi[10], Massimo Galli[10], Claudio Mastroianni[11], Alberto Matteelli[5], Francesco Mazzotta[12], Mauro Moroni[10], Giorgio Palù[13], Massimo Puoti[14], Vincenzo Puro[1], Giuliano Rizzardini[15], Evangelista Sagnelli[16], Fredy Suter[17], Stefano Vella[18], Adriano Lazzarin[6] for the Italian HIV Guidelines Working Group*

[1]National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy;
[2]Nadir Onlus Foundation, Rome, Italy; [3]University of Tor Vergata, Rome, Italy; [4]University of Bari, Bari, Italy;
[5]University of Brescia, Brescia, Italy; [6]San Raffaele Scientific Institute, Milan, Italy;
[7]San Paolo Hospital, University of Milan, Milan, Italy; [8]University of Turin, Turin, Italy;
[9]Istituto Superiore di Sanità, National AIDS Centre, Rome, Italy; [10]University of Milan, Milan, Italy;
[11]S.M. Goretti Hospital, La Sapienza University, Polo Pontino, Latina, Italy; [12]S. M. Annunziata Hospital, Florence, Italy;
[13]University of Padua, Padua, Italy; [14]Niguarda Hospital, Milan, Italy; [15]L. Sacco Hospital, Milan, Italy;
[16]University of Naples, Naples, Italy; [17]Ospedali Riuniti di Bergamo, Bergamo, Italy;
[18]Istituto Superiore di Sanità, Department of Therapeutic Research and Medicine Evaluation, Rome, Italy

**The complete members of the Italian HIV Guidelines Working Group are listed in the acknowledgment session.*

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INTRODUCTION

This short version complies with the intention expressed in the methodological introduction to the full text *Italian Guidelines for the use of antiretroviral drugs and the diagnostic-clinical management of people with HIV-1 infection*. By definition, this version should not be considered completely exhaustive with respect to the full text version of the Guidelines, that are available at web site: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1301_allegato.pdf.

The aim of this version is simply to render certain concepts expressed in the document more usable, by specific circulation in booklet form, inviting the reader to refer to the extended version for further information and full details.

It was decided not to discuss *in toto* in this version certain fundamental parts of the extended versions such as the populations requiring special attention (elderly, women, immigrants, children), the conditions requiring special attention (drug and/or alcohol addiction, detention) or the situations requiring special attention (transplants).

For all these populations, conditions or situations, it should be referred at the full text version of the Guidelines.

Lastly, it was decided to refer the reader to the extended version for all bibliographic citations, except for the essential references cited at the end of this version.

Corresponding author
Adriano Lazzarin, MD
San Raffaele Scientific Institute
Department of Infectious Diseases
Via Stamira D'Ancona 20 - 20127 Milano, Italy
E-mail: adriano.lazzarin@hsr.it

TABLE 1 - *Degree of recommendation and level of evidence*

Degree of recommendation	
A	Highly recommended.
B	Moderately recommended.
C	Optional.

Level of evidence	
LEVEL I	The data are collated from at least one controlled, randomized study with sufficient potency or from s meta-analysis of controlled studies.
LEVEL II	The data are collated from non-randomized studies or from cohort observational studies.
LEVEL III	Recommendation based on case reviews or agreement among experts.

PATIENT ASSESSMENT AND PREPARATION

The initiation of combination antiretroviral therapy (cART) should be considered a crucial moment in the management of HIV infection which requires:
- particular competency of the attending physician;
- comprehension and agreement on the part of the patient.

Physician-patient communication and the quality of their relationship can influence acceptance of this new phase. In particular, the capacity to establish a rapport of trust in the relationship conditions the willingness of the patient to accept and agree to the therapeutic prescription.
It is thus fundamental to assess the individual's degree of receptiveness, which depends on social, cognitive and emotional variables, and affects the capacity to understand the the information provided. It is emphasized that information skills depend not only on talking skills but also on the capacity to listen and understand.
Recommendations [AIII]:
- Offer the patient an interview in private.
- Guarantee the time necessary for comprehension, listening to and answering the patients' questions.
- Explain in detail why it is important and/or necessary to commence HAART.
- Inform the patient of the treatment options with a discussion of the benefits and risks of each approach.

VIRO-IMMUNOLOGICAL DIAGNOSTICS

The diagnosis of chronic HIV-1 infection is defined by the presence of HIV-1 antibodies, confirmed by immunoblotting.
The plasma HIV-RNA concentration (viremia or viral load) is used as a surrogate marker and serves to forecast the risk of clinical progression of the infection (prognostic marker) and assess the degree of the therapeutic response (efficacy marker). The principal objective of combination antiretroviral therapy in all patients is a reduction in viremia to undetectable levels (undetectability), and the maintenance of virological suppression for as long as possible [AII]. To date, the guidelines suggest using a limit value of greater than 50 copies/mL as the criteria for virological failure assessment [AI].
The use of resistance tests is currently recommended both for the choice of the first line therapy [AII] and for the choice of alternative therapy in the case of virological failure [AI].

The use of genotype assays is preferable to phenotype assays. Resistance assays should be interpreted with the use of viral genetic sequences with management algorithms (virological interpretation). Ideally, resistance assays should be interpreted by clinician with experience in utilizing additional parameters in the assessment, such as previous resistance tests, immunovirological and therapeutic data (virological and clinical interpretation). The best interpretation can be obtained in the latter conditions [AII]. An additional assessment with phenotype tests may prove useful for patients with complex resistance situations [BIII].
The data available to date indicate the utility of genotype or phenotype test for assessment of the prevalent viral strain for the purpose of using CCR5 antagonists [AII]. The simplicity of performance, lower costs, and the reliability of the test favour the genotypic assay [BII].
Quantification of the CD4+ lymphocyte count is an essential prognostic marker. The CD4 count determines the indication for initiation of antiretroviral therapy as well as the intiation or suspension of prophylaxis of opportunistic infections [AI].
The CD4+ count should be repeated 1 month after commencing antiretroviral therapy and, subsequently every 3-4 months in the stable phase. In patients with unsatisfactory immunological recovery (<50-150 cells/μL per year), immunological monitoring should be more frequent (2/3 months) [BI].
The percentage CD4+ count must be assessed together with the total CD4+ count as an immune system function marker (CD4+ percentages below 14% are associated with an increased risk of opportunistic infections, approximately equivalent to a CD4+ count of <20 cells/ L) [AII].

WHEN TO START

TABLE 2 - *When to start in patients with acute infection.*

Condition	*Recommendation for treatment*	*Strength/evidence*
Acute infection or recent seroconversion	Not recommended	
Acute infection with severe symptomatology	Highly recommended*	[AII]
*If therapy is initiated, inclusion in a controlled clinical study is recommended where possible [BIII]		

TABLE 3 - *When to start in patients with chronic infection.*

Clinical condition	*Lymphocyte T CD4+ count*	*Recommendation for treatment*	*Strength/evidence*
AIDS	Any value	Highly recommended	[AI]
HIV-related diseases (group B of 1993 CDC definition)	Any value	Highly recommended	[AII]
Pregnancy	Any value	Highly recommended	[AI]
HIV-associated nephropathy (HIVAN)	Any value	Highly recommended	[AII]
Non AIDS-defininig cancers	Any value	Highly recommended	[AII]
HIV-associate neurocognitive disorders (HAND)	Any value	Highly recommended	[AII]
Chronic HBV hepatitis requiring treatment*	Any value	Highly recommended with agents active against both HIV and HBV	[AII]
Elevated risk of secondary HIV transmission	Any value	Moderately recommended only in the case of a motivated patient	[BII]

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Clinical condition	*Lymphocyte T CD4+ count*	*Recommendation for treatment*	*Strength/evidence*
Asymptomatic	CD4+: ≤201-350 cells/µL	Highly recommended	[AII]
Asymptomatic	CD4+: 351-500 cells/µL	*Moderately recommended* in all patients *Highly recommended* in the presence of: a) HIV-RNA >100.000 copies/mL b) decrease in CD4+ >100 cells/ L per year c) age >50 years d) chronic hepatitis from HCV *Moderately recommended* in the case of: e) elevated cardiovascular risk: diabetes mellitus or previous cardiovascular event, or elevated risk in the next 10 years (estimate with *Framingham* algorithm)	[BII] [AII] [AII] [AII] [AII] [BIII]
Asymptomatic	CD4+ >500 cells/µL	Not recommended, except in cases of a highly motivated patient and/or in the presence of the factors indicated above at items a), b), c), d), e), where it is optional.	[CII]
*In cases in which there is indication of HBV treatment by nucleotide/nucleoside analogues.			

TABLE 4 - *Timing of initiation of antiretroviral therapy in patients with AIDS or non-AIDS defining neoplasias (treatment Highly recommended [AI]).*

Clinical condition	*Timing of commencement of antiretroviral therapy*	*Strength/evidence (referred to the timing of commencement of arv therapy)*
- Multifocal progressive leukoencephalopathy - HIV encephalopathy - Wasting syndrome - Enteritis from *Cryptosporidium* or *Microsporidia*	Immediate initiation highly recommended	[AII]
Pneumonia from *P. jiroveci*	Highly recommended initiation within 2 weeks of diagnosis	[AI]
Pulmonary tuberculosis	Highly recommended initiation within 3 months of anti-tubercular therapy	[AI]
Tubercular meningitis	Moderately recommended initiation after 2 months of 4 drug anti-tubercular therapy	[BI]
Cryptococcal meningitis	Highly recommended initiation upon completion of induction therapy for opportunistic infection	[AI]
Disease from atypical mycobacteria	Optional, where possible, initiation within 4 weeks of treatment for mycobacteriosis	[CIII]
CMV Disease	Optional, where possible, initiation upon completion of induction therapy for opportunistic infection	[CIII]
Patients with neoplasia	Highly recommended immediate initiation and, in all cases recommended prior to initiation of chemotherapy	[AII]

WHAT TO START WITH

The choice of initial therapy in patients with HIV must be tailored to:

1. Available data on the characteristics of the different agents and drug combinations (virological and immunological efficacy, conformulation/convenience, toxicity and tolerability, genetic barrier, prior clinical use).
2. Factors regarding the overall clinical status, genetic factors, and characteristics of the patient including:
   - Comorbidities (cardiovascular disease, hepatic, renal disease, neuro-cognitive disorders, psychiatric illness, concurrent infections and/or conditions such as drug abuse/dependence, etc.);
   - Potential adverse effects of the drugs used;
   - Potential drug-drug interactions;
   - Current or pregnancy potential;
   - Genotype resistance test;
   - Likelihood of adherence to treatment;
   - Acceptability of regimen (number of pills, number of administrations, assumption modality);
   - CD4+ lymphocytes count, if use of nevirapine is considered;
   - HLA-B 5701, if use of abacavir is considered.

TABLE 5 - *Conditions for classification of drugs and combinations.*

Conditions for classification of drug/combination
Drug/combination satisfying the majority of the following conditions: it is considered "*standard of care*"; in at least one randomized study it has shown to be at miniumum non inferior to "*standard of care*"; is compact/ convenient; it has a favourable toxicity and tolerability profile; it has demonstrable extensive clinical use.
Drug/combination which does not satisfy all the first choice criteria but which may represent, in specific cases, the best choice for a given patient (profiles of toxicity, pharmacological interactions with concomitant treatments).
Drug/combination considered efficacious, in cases where the patient does not tolerate or is unable to take first choice or alternative drugs/associations.
To date, data in the scientific literature reports, almost exclusively, the results obtained with combination regimens consisting of: a backbone of nucleos(t)ides (NRTI) and a base of a third drug from another class. Indications for the choice of drugs constituting the backbone may be determined on the basis of available coformulations rather than the single drug.

To date, data in the scientific literature reports, almost exclusively, the results obtained with combination regimens consisting of: a *backbone* of nucleos(t)ides (NRTI) and a *base* of a third drug from another class. Indications for the choice of drugs constituting the ***backbone*** may be determined on the basis of available coformulations rather than the single drug.

TABLE 6 - *Backbone nucleos(t)ide. First choice and alternatives.*

Choices	*Pharmacological association [Strength/evidence]*	*Comment*
First Choice	TDF/FTC* [AI]	Superior to ZDV/3TC; co-formulated; QD.
	TDF/3TC* [BI]	Only non-inferior to d4T/3TC, greater risk of resistances at failure compared to TDF/FTC (but not by direct comparison); non co-formulated; QD.
	ABC/3TC**[BI]	Only non-inferior to ZDV/3TC; inferior to TDF/FTC in presence of elevated viral loads; in patients with viremia greater than 100,000 copies/mL it must not be used in combination with ATV/r or EFV, but only with LPV/r; lack of data on association with DRV/r and RAL; higher CV risk; co-formulated; QD.
Alternative	AZT/3TC [BI]	Less effective; greater toxicity; lower genetic barrier; lack of data on association with DRV/r, ATV/r and RAL; co-formulated; non QD.

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Choices	*Pharmacological association [Strength/evidence]*	*Comment*
Acceptable	ddI/3TC or FTC*** [CI]	ddI/3TC/EFV non-inferior to ZDV/3TC/EFV; greater toxicity than ddI, absorption significantly determined by food; non co-formulated; QD.

*Tenofovir should not be used in patients with renal insufficiency.
**Abacavir can only be used in HLA-B*5701 negative patients (screening recommended [AI]) and clinical HSR surveillance must be maintained in these patients; use with care in patients at elevated risk of cardiovascular disease (*Framingham risk score* > 20%): even though observational data on increased cardiovascular risk with ABC not consistent and the biological mechanism insufficiently clarified; do not initiate concomitant treatment with nevirapine due to augmented risk of hypersensitivity reactions (HSR).
***Didanosine + FTC/3TC only in association with EFV; with ATV excess of early virological failures; long-term mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis), hepatic and endothelial (excess of myocardial infarction, non cirrhotic portal hypertension); not indicated in conjunction with ribavirin (see HIV/HCV co-infection chapter).

TABLE 7 - *Third drug, first choice.*

In regards to choice of class for the third agent, consideration should be given to long-term efficacy data, the genetic barrier to resistance and the long-term sequencing strategy.

Choices	*Drug [Strength/ evidence]*	*Comment*
First Choice	EFV* (600 mg) [AI]	*Standard of care* in the majority of randomized clinical studies in which it has consistently shown equivalence or superiority; neuro-psychiatric disturbances in the first 12 weeks administration; QD.
	ATV/r (300/100 mg QD) [AI]	Elevated tolerability. Non-inferior to EFV; non-inferior to LPV/r with lower gastrointestinal toxicity and dyslipidaemia. Lack of data on the association with ZDV/3TC; hyperbilirubinaemia; QD.
	NVP** (400 mg) [BI]	Criterion of non inferiority to EFV not reached; non-inferior to ATV/r (48 weeks) but greater toxicity; best lipid profile with respect to ATV/r; equivalent to LPV/r (>48 weeks) but greater toxicity. Lack of data on the association with ABC/3TC. BID; QD optional (not authorized in Italy).
	DRV/r (800/100 mg QD) [BI]	Limited use in naïve patients. Non-inferiority demonstrated only with respect to LPV/r; lack of comparative studies with EFV or ATV/r. Lower gastrointestinal toxicity and dyslipidaemia than LPV/r. Lack of data on the association with ABC/3TC and ZDV/3TC.
	LPV/r*** (800/200 mg QD or 400/100 BID) [BI]	Inferior to EFV at 96 weeks. *Standard of care* in the majority of comparative studies with other PIs; sole co-formulated PI; greater toxicity; 200 mg of RTV; greater dyslipidaemia and gastrointestinal disturbances than DRV/r and ATV/r; higher number of pills; BID (QD non-inferior to BID but only 48 weeks; QD inferior to DRV/r QD).
	RAL (400 mg BID) [BI]	Limited use in naïve patients; non-inferior to EFV with fewer adverse events and dyslipidaemia; Lack of data on the association with ABC/3TC and ZDV/3TC; BID.

*EFV must not be used during first trimester of pregnancy, in women planning pregnancy or who may become pregnant due to lack of contraceptive use.
**NVP must not be used in women with CD4+ >250 cells/µL or in men with CD4+ >400 cells/µL (higher risk of hepatotoxicity and/or cutaneous *rash*); in the first two weeks of therapy utilize the induction dose 200 mg/day. Some pilot studies indicate excess early virological failure with use of TDF+3TC+NVP QD: this combination should therefore be avoided, with the TDF/FTC+NVP combination, both QD and BID were found efficacious in randomized studies. Use with care in patients with hepatic viral co-infection.
***LPV/r 400/100 BID is the first choice therapy in pregnant women.

TABLE 8 - *Third drug, alternative, acceptable choices*

Choices	*Drug [Strength/ evidence]*	*Comment*
Alternative	FPV/r* (700/100 mg BID) [BI]	Non-inferior to LPV/r BID at 96 weeks with same toxicity profile; BID, 200 mg RTV and higher number of pills; QD not authorized in Italy.
	SQV/r (1000/100 mg BID) [BI]	Non-inferior to LPV/r (but less hypertriglycerideamia), but with only 48 weeks follow-up; 200 mg RTV; higher number of pills; BID.
Acceptable	ATV** (400 mg QD) [CI]	Non-inferiority study with small sample size does not confirm non-inferiority to ATV/r at 96 weeks; greater virological failures; studied only in association with d4T+3TC.
	Maraviroc*** [CI]	Non-inferior to EFV only in one post-hoc analysis; BID; studied only with AZT+3TC.

*FPV/r 1400/200 mg QD [BI]) 48 week studies compared with NFV, daily dosing not authorized in Italy; FPV/r 1400/100 mg QD [BI]) small study, dosing not authorized in Italy.
**ATV without ritonavir not authorized in Italy; not to be used in any case without ritonavir booster when in concomitant use with tenofovir (except where plasma levels can be verified by TDM, see specific chapter) and/or efavirenz. The panel has decided to await new data before making a definitive recommendation.
***Maraviroc not registered in Italy for first line use. In naïve patients it demonstrated non-inferiority at 96 weeks against efavirenz in only one post-hoc analysis. The agent was studied exclusively in association with AZT+3TC at a dosage of 300 mg BID. Good efficacy is to be expected with a non-thymidine analogue backbone. Nevertheless, the panel has decided to await new data before making a definitive recommendation.

TABLE 9 - *Comparison of virological and immunological efficacy, convenience and genetic barrier of different antiretroviral regimens used in the treatment of naïve patients (first and alternative choice).*

NUCLEOS(T)IDIC BACKBONE					
Rank	*Virological efficacy*	*Immunological efficacy*	*Compactness/convenience (number of pills and administrations, co-formulation)*	*Extensive clinical use*	*Genetic barrier (lower frequency of resistance at failure)*
1	TDF/FTC TDF+3TC	TDF/FTC TDF+3TC ABC/3TC	TDF/FTC ABC/3TC	TDF/FTC TDF+3TC ABC/3TC AZT/3TC	TDF/FTC ABC/3TC
2	ABC/3TC	ddI+3TC AZT/3TC	TDF+3TC ddI+3TC	ddI+3TC	TDF+3TC AZT/3TC ddI+3TC
3	AZT/3TC ddI+3TC [3, 14]		AZT/3TC		
THIRD DRUG					
1	EFV ATV/r DRV/r RAL	ATV/r, LPV/r, DRV/r, FPV/r, SQV/r	EFV	EFV LPV/r ATV/r	DRV/r ATV/r LPV/r FPV/r SQV/r
2	LPV/r FPV/r SQV/r NVP (48 weeks, non inferior to ATV/r, equivalent to LPV/r)	EFV, NVP, RAL SQV/r (48 weeks)	ATV/r	NVP FPV/r SQV/r	EFV NVP RAL

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Rank	*Virological efficacy*	*Immunological efficacy*	*Compactness/convenience (number of pills and administrations, co-formulation)*	*Extensive clinical use*	*Genetic barrier (lower frequency of resistance at failure)*
3			NVP*, DRV/r RAL, LPV/r	DRV/r RAL	
4			FPV/r, SQV/r		
*If administered QD, rank 2					

HOW TO CONTINUE: SIMPLIFICATION

Therapeutic simplification involves the modification of at least one drug in the regimen and is intended to improve quality of life by increasing tolerability, reducing number of pills/administrations, and reducing pharmacological interactions. By improving adherence, simplification also intends to reduce the risk of therapeutic failure. Reduced medium to long-term toxicities is a possible indication for simplification of therapeutic regimens. This section only considers simplification in conditions of virological suppression (HIV-RNA <50 copies/mL).

Indications for simplification

- Documented toxicity.
- Presence of side-effects.
- Planned pregnancy.
- Desire to simplify therapy.
- Current regimen no longer recommended.
- Prevention of long-term toxicity (*pre-emptive switch*).
- Current therapy may worsen co-morbidities or clinical manifestations linked with aging.
- Interactions with other drugs.
- Indication to treat other infections (TB, HBV, HCV, etc.).

Simplification strategies in patients with stably suppressed viremia

- Intra-class simplification in the case of side-effects to single agents, including improvement dyslipidaemia and/or lipodystrophy.
- Simplification to once daily administration of NRTI or PI/r administered BID in order to improve adherence.
- Simplification from PI/r to EFV, NVP or RAL to prevent or improve metabolic toxicity and improve adherence (only in cases with no prior virological failure and full activity of NRTIs utilized).
- Simplification to monotherapy with PI/r (DRV/r and LPV/r with reintroduction of the 2 NRTIs in the case of rebound to low viremia) in the case of toxicity or reduced NRTI tolerability: only in selected patients with no history of virological failure, with undetectable viremia (<50 copies/mL) for at least 6 months, good immunological recovery and CD4+ nadir >100 cells/μL, on treatment with PI/r and without PI resistance mutations as determined prior to initiation of antiretroviral treatment. In all cases, close virological monitoring is required for early assessment of possible failure.
- Simplification from enfuvurtide to raltegravir for ease of administration and elimination of cutaneous side-effects in patients with no previous treatment experience with integrase inhibitors.

MANAGEMENT OF THERAPEUTIC FAILURE

Despite the efficacy of current antiretroviral treatment, a measurable proportion of patients experience therapeutic failure due to a suboptimal virological response (virological failure), unsatisfactory immunological response (immunological failure) and, to a lesser extent, clinical progression (clinical failure). Clinical failure is defined by the onset of HIV-related clinical events in patients on antiretroviral therapy for at least three months, after the exclusion of immune reconstitution syndrome. Immunological failure may be defined as a failure to recover and/or maintain (a normal?) CD4+ lymphocytes count, despite virological suppression. Virological failure is defined by lack of suppression of HIV viremia to values below 50 copies/mL of plasma HIV-RNA (undetectability) 24 weeks after treatment initiation or as a rise in viral replication (rebound), confirmed by two consecutive measurements in patients who had previously achieved complete viral suppression.

TABLE 10 - *Recommendations for accurate, early assessment of virological failure.*

Condition	*Recommendation*
Patients with residual low-level viremia (1-49 copies/mL).	Documentation of residual low-level viremia no longer satisfies the criteria for diagnosis of virological failure. On the basis of the data available there is no indication for modification of the current regimen [AIII].
Patients with viral blips (50-1000 copies/mL), isolated, non consecutive, alternating with undetectable viral load measurements.	Investigate adherence, potential pharmacological interactions, consider possible variability in the HIV-RNA test. Modification of the antiretroviral regimen is not necessary [AII].
Patients with viral blips (50-1000 copies/mL) persistent, consecutive, progressively rising, genotype non determinable.	There is no clear guidance in the literature on the appropriate management of these patients, although active, persistent viral replication is evident. It is reasonable to undertake genotyping and consider modification of the current antiretroviral regime [BII].
Patients with viremia >1000 copies/mL and absence of mutations in the genotypic resistance test performed.	Investigate adherence, consider resumption of the same regimen monitoring the virological response after 4 weeks and repeating genotype for early identification of emergence of resistant viral variants [BIII]. In patients on unboosted protease inhibitor therapy, consider immediate introduction of low doses of ritonavir as a pharmacokinetic booster [BII].
Patients with viremia >1000 copies/mL and mutations in the genotype test performed.	Modify the current antiretroviral regime [AII].

TABLE 11 - *Useful considerations when deciding on a new antiretroviral regimen in patients with virological failure.*

In a patient with virological failure, a new antiretroviral regimen must include at least 2, preferably 3 fully active drugs [AII]. In the case of first failure, it is advisable to choose drugs from classes that have not been used before.
With standard tests, the most recent genotype may not detect certain archived mutations. All of the patient's previous genotypic and phenotypic assays must be taken into consideration (when deciding on the appropriate choice of a new regimen); even agents to which the patients has never been exposed may not be fully active.
Consider all potential negative pharmacological interactions with the new regimen; a drug never taken before is not always a fully active drug when included in a new therapeutic regimen.
In patients who do not have three fully active drugs available, consider that some antiretroviral drugs (e.g. NRTIs) can contribute to the efficacy of the new regimen with partial antiviral activity, albeit in the presence of resistance, while for other drugs (e.g.: enfuvirtide, NNRTIs, raltegravir) no partial antiviral activity has been demonstrated.
Certain factors are associated with a more favourable virological response, irrespective of the type of regimen used (e.g.: low-level viremia and elevated CD4+ at the time of regimen modification, use of a drug from a new class, increasing number of active drugs and, therefore, GSS and PSS).

TABLE 12 - *Recommended sequential regimens as determined by failed first line therapy.*

First regimen	*Second regimen*
2 NRTI + NNRTI	2 NRTI* + PI/r
2 NRTI + PI/r	2 NRTI* + PI/r*
2 NRTI + PI	2 NRTI* + PI/r*
3 NRTI	*1 NRTI + 1 PI/r + 1 NNRTI *2 NRTI + 1PI/r 1PI/r + 1 NNRTI - 1PI/r + 1 INI - 1 PI/r + 1 CCR5 inhibitor
* = Chosen on the basis of resistance assay.	

TABLE 13 - *Management of virological failures subsequent to the first and use of new classes of drugs.*

Situation	*Choice*
Availability of at least 2 active drugs*	Change the regimen as soon as possible. If possible include high genetic barrier drugs in the regimes (new boosted protease inhibitors) in combination with other agents of different classes chosen on the basis of resistance test results.
Availability of 1 active drug only*	The most fragile situation, the decision to modify antiretroviral therapy must take into account the immediate risk of clinical progression, the risks associated to maintenance of the current regimen and the probability of virological success of the subsequent regime in the medium term. A maintenance regimen may be reasonable while awaiting the availability of another active drug.
Absence of active drugs	Determine the optimal maintenance regimen.
**of all agents available, in the market or in early access protocols.*	

ADHERENCE AND QUALITY OF LIFE

Optimal adherence to antiretroviral drugs must always be pursued in order to obtain and maintain both the viro-immunological and clinical success of treatment [AII]. In the clinical setting, the patient's self-reported adherence, if investigated with a non-judgemental, routinized and structured fashion, is the most suitable method to measure adherence and institute longitudinal monitoring for early identification of specific barriers to adherence [AII]. Other objective methods, such as assessment of antiretroviral refill dates, pill counts, and plasma drug concentration monitoring may be utilized as adjunctive information to assess patient adherence [BII]. Simplified antiretroviral dosing with fixed-dose combinations has been shown to promote adherence to the antiretroviral therapy [AI].
In the clinical setting, observation of non-adherence behaviour requires intervention strategies [AI]. Identification of the most appropriate intervention is based on the experience of the medical-nursing staff and is based on a "tailored" approach combining strategies related to the antiretroviral management with educational and behavioural approaches providing support to the patient [BI]. The improvement in quality of life related to health is a primary objective of antiretroviral therapy. It is therefore necessary to include the use of patient-centered strategies in the clinical care of the patient. Ongoing monitoring of patient-centered outcomes is recommended in clinical centres, with the same frequency as standard clinical examinations [AII].

PHARMACOLOGICAL MONITORING

Definition of TDM

Therapeutic monitoring of plasma drug concentrations (TDM - Therapeutic Drug Monitoring) is a useful adjunct for individualizing therapy, especially when utilzing agents with a clear correlation between concentration and therapeutic and/or toxic effect, a limited therapeutic margin and wide inter-individual pharmacokinetic variability.

TABLE 14 - *Clinical scenarios of possible use of TDM.*

Scenario	*Strength/evidence*
Significant alterations of gastroenteric, hepatic or renal function	[CIII]
Pregnancy	LPV/r, SQV/r [CIII]
Previous failures with resistant virus	PI with use of IQ [CII]
Concentration-correlated toxicity	IDV/r [BII], EFV [CII], ATV [CIII]
Non-conventional dosing schemes	[CIII]
Treatment adherence	[CIII]
Pharmacological interactions	[BIII]

Interactions

The management of pharmacological interactions is the clearest clinical indication for use of TDM [BIII]. Different antiretroviral drug types or classes (NNRTI, IP, MVC) are associated with significant pharmacological interaction as they are, to various extents, substrates, inhibitors or inducers of the P450 cytochrome (in particular the CYP3A4 isoenzyme, but also CYP2B6, CYP2C9, CYP2C19) and P glycoprotein. The N(t)RTI, ENF and RAL have differentiated metabolic profiles and therefore have limited or low potential for interaction. Refer to specific sites (*first of all* **www-hiv-druginteractions.org**) for an exhaustive discussion of information pertaining to management of pharmacological interactions.

TABLE 15 - *Principles of TDM use in the management of pharmacological interactions.*

NNRTI, PI and MVC have a higher risk of pharmacological interaction as substrates, inhibitors or inducers of the P450 cytochrome system and P glycoprotein.
N(t)RTI, ENF and RAL have limited or low potential for interaction.
The extent of a known interaction may be unpredictable in individual cases [CIII].
The sum of several simultaneous pharmacological interactions is often difficult to predict [CIII].
The extent of the interaction may have different specific weights and effects depending on the clinical variables of the single case [CIII].
A pharmacological interaction may be unpredictable and must be suspected in the case of unexpected clinical and therapeutic events [CIII].

PHARMACO-GENETICS

TABLE 16 - *Principles of use of genetic testing for the HLA-B*5701 allele.*

Highly recommended before starting antiretroviral therapy containing ABC [AI].
In negative patients clinical monitoring is recommended in all cases within the first 6 weeks of treatment as the possibility of abacavir associated HSR cannot be completely excluded [CIII].
The test should be performed at baseline in all newly infected patients in order to register data in the patients' clinical records for future use [CIII].

NON-INFECTIOUS COMORBIDITY

General principles

The non-infectious pathologies associated with HIV infection are the most frequent symptomatic manifestations in HIV-infected persons on antiretroviral therapy.

These derive from the interaction of risk factors relative to host, virus, and drug [BII]. Their clinical relevance affects:

- prognosis [AI];
- choice or modification of the antiretroviral drugs [AII];
- multidisciplinary patient management [AIII].

These comorbidities manifest in progressive organ damage leading to end-stage organ failure:

- End-stage organ failure determines patient morbidity and mortality [BII].
- They may be diagnosed by functional or structural tests with the capacity to detect disease in the asymptomatic stage [BII].
- Multiple comorbidites are physiological during aging and HIV infection is associated with a process of premature aging the pathogenetic mechanisms of which are only partially understood.

Risk factors associated with HIV infection are related to genetic and environmental factors which, in turn, affect lifestyle.

The recognition and correction of deleterious lifestyle choices are the most effective interventions for prevention and treatment of non-infectious comorbidities.

Factors related to HIV infection include immunological damage (*immunodeficit* and immune deregulation) and by a state of systemic inflammation associated with accelerated the cellular and organ senescence.

Undetectable HIV viremia does not eliminate the excess risk associated with HIV disease. Co-infections (hepatitis viruses, herpes viruses, etc.) are additional risks for non-infectious pathology.

The increased risk of specific organ damage associated with cumulative or current antiretroviral exposure occurs through mechanisms which have not been fully elucidated.

The table below shows the main risk factors for non-infectious comorbidites associated with HIV infection considered in these guidelines [AIII].

TABLE 17 - *Risk factors for non-infectious comorbidities associated with HIV infection.*

	Heart	*Kidney*	*Bone*	*Liver*	*Cancers*	*Lipodystrophy*
Age	✔	✔	✔	✔	✔	✔
Sex	✔		✔	✔		✔
Diabetes	✔	✔	✔	✔		✔
Hypertension	✔	✔				
Dyslipidaemia	✔	✔	✔	✔		✔
Family history	✔	✔	✔		✔	
Waist circumference	✔			✔		✔
Vit D/PTH	✔	✔	✔	✔	✔	✔
Smoking	✔	✔	✔	✔	✔	✔
CD4+				✔	✔	✔
HIV VL	✔	✔				
ARV	✔	✔	✔	✔	✔	✔

Screening for non-infectious comorbidities associated with HIV infection

Screening for non-infectious comobidities is an integral part of comprehensive clinical assessment in all HIV infected patients [AII]. Screening must be periodic and should be repeated, in all patients, before starting antiretroviral therapy or when changing antiretroviral management strategy [AIII].

TABLE 18 - *Screening strategies for non-infectious comorbidities associated with HIV infection.*

	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with cart*	*Follow-up freq. without cart*	*Comments*
Anamnesis	Prior and current non-infectious pathologies.	+	+			Assessment to be repeated if patient transferred to other care centre
	Family history (e.g. early cardiovascular disease: indicates cardiovascular events, diabetes, hypertension, chronic kidney disease)	+	+			Early cardiovascular disease - cardiovascular events in first degree family members: males <55 years, females <65 years
	Concomitant pharmacological therapies	+	+	at each visit	at each visit	

→

	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with cart*	*Follow-up freq. without cart*	*Comments*
Anamnesis	Current lifestyle: - alcohol consumption (toxic alcohol damage is expressed in consumption exceeding 30 grams/day in males and 20 grams in females) - smoking - diet - physical activity	+	+	Every 6-12 months	once a year	More frequent discussion with the patient of healthy lifestyle and habits is recommended
Body composition	Measurement of body mass index and waist circumference	+	+	once a year	once a year	Objective examination for lipodystrophy must be segmental, where possible using assessment methods for the diagnosis of the lipo-atrophy and lipo-hypertrophy. The objective tools for of measurement of lipo-atrophy and lipo-hypertrophy include DEXA (with measurement of the fat mass in the limbs), abdomen CT (with measurement of visceral subcutaneous fat) and ultrasonography assessment of the depth of subcutaneous fat in the limbs and cheeks [BIII]
	Clinical assessment of lipodystrophy	+	+	once a year	once a year	
Cardiovascular disease	Assessment of overall risk	+	+	once a year	once a year	Using algorithms such as Framingham (http://hp2010.nhlbihin.net/atpiii/CALCULATOR.asp?usertype=prof), PROCAM (http://www.chd-taskforce.com/procam_interactive.html), Raynolds (http://www.reynoldsriskscore.org), SHAPE (http://www.shapesociety.org/your_levels_of_risk/) and in personal clinical evaluation
	ECG	+				
Hypertension	Blood pressure	+	+	once a year	once a year	
Dyslipidaemia	TC, HDL Col, LDL Col, TG	+	+	once a year		

	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with cart*	*Follow-up freq. without cart*	*Comments*
Diabetes mellitus	Serum glucose	+	+	Every 6-12 months		Consider oral glucose load test if fasting glycaemia values rare repeatedly between 110-125 mg/dl
Liver disease	Risk assessment, ALT/AST, GGT	+	+	Every 3-6 months	Every 6-12 months	Frequency of checks must increase before and during treatment with hepatotoxic drugs
	Liver ultrasonography in patients with liver enzyme elevation	+	+	once a year	once a year	
Kidney disease	Risk assessment	+	+	once a year	once a year	
	eGFR estimated possibly with the CKD-EPI calculator or alternatively MDRD or Cockroft-Gault	+	+	Every 3-6 months	Every 6-12 months	Frequency of checks must increase in the presence of risk factors for chronic kidney disease and/or before and during treatment with nephrotoxic agents
	Urinalysis for proteinuria and plasma phosphate levels	+	+	once a year	once a year	Every 6 months with estimated eGFR <60 ml/min; with proteinuria ≥1 + and/or estimated eGFR <60 ml/min, measure protein/creatinine in urine. In patients starting a tenofovir-containing regimen the initial assessment including plasma phosphate level must be conducted after 2-4 weeks and every 3-6 months thereafter
Bone disease	Height measurement	+	+	every 2 years	every 2 years	In the case of a loss of more than 3cm in height, lateral spine Xrays (thoracic) are indicated [AII]
	Assessment of major risk factors for osteoporosis	+	+	once a year	once a year	
	Estimate of risk of fractures in subjects aged >40 years with FRAX®	+	+	Every year	every year	

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	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with cart*	*Follow-up freq. without cart*	*Comments*
Bone disease	Vitamin D dosage	+		twice a year	twice a year	Preferably to be performed in the autumn and spring, not necessary if nutritional supplementation given [AII]
	Examination of bone mineral metabolism (at least 1 re-absorption marker and 1 deposit marker) and PTH	+		Every year	Every year	[AII]
	DXA scan of the lumbar spine and hip or densitometry surrogate tests		+	every 2 years	every 2 years	DXA is indicated when, in addition to HIV, at least 2 of the following risk factors are present: hypogonadism, family history of fractures, BMI <19 kg/m^2, hypovitaminosis D, smoking, sedentary lifestyle, history of low impact fractures, advanced age, female sex, menopause and/or amenorrhea, habitual alcohol excess (>3 units/ day), steroids exposure for >3 months [BIII]. DXA has the advantage of providing objective anthropometric measurements for the diagnosis of lipodystrophy [BIII]

Assessment of the risk of toxicity associated with antiretroviral drugs

There are short- and medium-term toxicities linked with the use of antiretroviral drugs. Continuous exposure to antiretroviral therapy reinforces the need for post-marketing pharmacological surveillance [BII].

HIV infection control through virological suppression is a required for reducing drug related toxicities [AI].

The principal toxicities attributable to different classes and single drugs, based on data from registration studies or significant cohort studies, are listed below.

TABLE 19 - *Principal toxicities attributable to different ARV classes and single drugs.*

	Rash - hypersensitivity	*Gastrointestinal*	*Hepatic toxicity*	*Cardiovascular*	*Bone/muscle*	*Renal toxicity*	*Nervous system*	*Lipodystrophy*	*Metabolic alterations*
NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X

→

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	Rash - hypersensitivity	*Gastrointestinal*	*Hepatic toxicity*	*Cardiovascular*	*Bone/muscle*	*Renal toxicity*	*Nervous system*	*Lipodystrophy*	*Metabolic alterations*
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
PI		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Fusion inhibitors									
ENF	X								
Integrase inhibitors									
RAL					X		X		
CCR5 Inhibitors									
MVC			X						

General principles of treatment of non-infectious comorbidities

TABLE 20 - *Principles of intervention for main modifiable factors.*

Interventions	*Principles*
Smoking cessation	Identify the motivational aspects for discontinuing smoking The short-term benefits are: - monetary savings - increased perception of flavours - improved skin trophism - reduction of dyspnea.

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Interventions	*Principles*
Smoking cessation	The long-term benefits are: - prevention of chronic obstructive pulmonary disease (COPD) - coronary artery disease and stroke - lung cancer Instruments of proven utility for smoking cessation: - refer to specialist anti-smoking centres - nicotine substitute products
Diet	Nutritional counselling: - Maintain the balance between calorie input and energy consumption - Moderate intake of saturated fats, cholesterol and refined carbohydrates - Limit alcohol consumption to <20 gr/day for females and <30 gr/day for males - Reduce total fat intake to <30% and cholesterol intake to <300 mg/day - Consume many vegetables, fruit and fibre rich cereals - Introduce fish, poultry (no skin) and lean meat to the diet - Avoid alternating periods of strict diet and binges (so-called yo-yo dieting) Specialist nutritional intervention reserved for obese patients and those with wasting syndrome
Physical therapy	An active lifestyle is fundamental to prevent and treat obesity, hypertension and diabetes. Regular aerobic activity (e.g. 30 minutes of sustained walking at least 5 days a week) is useful to reduce the accumulation of visceral fat, maintain muscular strength and prevent osteoporosis. It is necessary to verify that the physical activity undertaken satisfies cardio-fitness requirements (adequate duration, adequate increment of cardiac frequency)

TABLE 21 - *Identification and management of patients at high risk of cardiovascular disease.*

<table>
<tr><td colspan="7">Identification of patients with high cardiovascular risk through:
1. Estimation of the risk of cardiovascular disease (CVD) with risk prediction charts or algorithms
2. Individual clinical assessment</td></tr>
<tr><td colspan="7">Advise on diet and lifestyle in all patients
Consider individualized modification of ARV therapy in patients with high CV risk</td></tr>
<tr><td colspan="7">Identification of modifiable risk factors</td></tr>
<tr><td>Smoking</td><td colspan="2">Blood pressure</td><td>Coagulation</td><td>Glucose</td><td colspan="2">Lipids</td></tr>
<tr><td rowspan="5"></td><td colspan="2">Start treatment if: systolic blood pressure (SBP) ≥140 or diastolic blood pressure (DBP) ≥90 mmHg (especially if 10-year CVD risk ≥20%)</td><td>Start treatment if: CVD present or age ≥50 and 10-year risk ≥20%</td><td>Confirm diagnosis of DM and start therapy if: HBA1c ≥6.5%</td><td colspan="2">Start treatment therapy if: CVD present or type II DM II or TC:HDL ratio >6 or 10-year risk ≥20%</td></tr>
<tr><td colspan="2">Target</td><td>Target - N/A</td><td rowspan="4">Target HBA1c <6.5%</td><td colspan="2">Target</td></tr>
<tr><td rowspan="3">If DM or CVD or CKD+proteinuria. BP <130/<80</td><td rowspan="3">Absence of DM and CVD, BP <140/<90</td><td rowspan="3">Treatment with acetylsalicylic acid 75-150 mg/d</td><td></td><td>Optimal</td><td>Standard</td></tr>
<tr><td>TC</td><td>155 mg/dL</td><td>190 mg/dL</td></tr>
<tr><td>LDL</td><td>80 mg/dL</td><td>115 mg/dL</td></tr>
</table>

Prevention and management of patients at high risk of hepatic damage

Prevention	*Management*
In the case of co-infection with Hepatitis C virus evaluate the possibility of treating this condition: treatment of Hepatitis C reduces the risk of "drug-induced liver injury" (DILI). Refer to the specific section of the guidelines for management of these cases. In obese patients and those with metabolic syndrome, ultrasonography to assess the presence of NAFLD. Computed tomography (CT) and magnetic resonance imaging (MRI) may be used for further diagnostics in selected cases. Modifying predisposing factors for NAFLD such as hyperglycaemia, dyslipidaemia, arterial hypertension, abdominal obesity, may reduce the evolution of liver disease and prevent drug-related hepatotoxicity. Among the modifiable predisposing factors consider HCV infection with genotype 3, which is associated with hepatic steatosis and an increased risk of drug-associated liver damage. In patients starting nevirapine: check liver enzymes at baseline, every two weeks for the first month, each month for the first three months, then every three months. Reassessment of current antiretroviral therapy: because liver damage - above all when linked with mitochondrial toxicity - may be clinically silent, it is important to evaluate the possibility of substituting older generation NRTI if present in current therapy.	Exclude other causes of liver enzyme elevation, in particular alcohol abuse, presence of co-infections with hepatitis viruses and interruption of treatment with 3TC, FTC and TDF in patients with chronic hepatitis B. In the case of liver enzyme elevation, if the patient is symptomatic with a clinical hepatitis or a concomitant rise in bilirubin, immediately discontinue all current treatment. Upon normalization, consider the use of antiretroviral drugs with minimal hepatic toxicity. In the asymptomatic patient, consider suspension of the drug in all patients with liver enzyme elevation 5-10 times the normal level. In the presence of both augmented liver enzyme elevation and of symptoms drug hypersensitivity reaction, suspend current treatment immediately. Re-administration of the same therapy may prove fatal.

Prevention and management of patients at high risk of bone disease

Prevention	*Management*
Lifestyles beneficial for the prevention and treatment of osteoporosis include: physical activity, daily consumption of 1 g of calcium and Vit D 800 UI/day with a weight loss and malabsorption prevention diet (BMI <18.5), smoking cessation and decreased alcohol consumption. A height loss of more than 3 cm suggests a diagnosis of vertebral fracture. The classic risk factors for osteoporosis include: hypogonadism, family history of fractures, BMI <19 kg/m^2, hypovitaminosis D, smoking, sedentary lifestyle, low impact fractures, advanced age, female gender, menopause and/or amenorrhea, habitual alcohol consumption of >3 units/day, steroids exposure for >3 months. Plasma levels of 25-OH vitamin D should be checked in all patients preferably in autumn and spring. Testing is not necessary in patients taking regular nutritional supplementation. Correct assessment of the bone structure cannot be separated from a study mineral metabolism.	The bone toxicity of tenofovir is expressed in particular in the first 12 months of therapy, especially if used in association with PI/r and in pre-treated subjects: in the case of alterations in renal function and/or of bone metabolism, and in the presence of valid, efficacious alternatives, it is advisable to assess options for treatment modification. There are no antiretroviral therapy simplification strategies of proven efficacy in the prevention or treatment of osteoporosis. For correction of hypovitaminosis D, cholecalciferol must be administered: two consecutive oral administrations of 300,000 UI each, preferably in spring and autumn, followed by a maintenance dose of oral cholecalciferol of 7,000 UI each week. In the case of hypovitaminosis, testing of plasma calcium, phosphate, alkaline phosphatase and PTH levels is indicated. Always supplement with calcium in the case of low alimentary intake.

Prevention and management of patients at high risk of lipodystrophy

Prevention	*Management*
For all patients with HIV infection, collection of anthropometric data including BMI, waist circumference, objective evaluation of adipose tissue redistribution is indicated, possibly with questionnaires.	Modification of antiretroviral therapy, replacing thymidine analogues, is the only measure proven to partially re-establish subcutaneous fat, with an average increase in total fat in the limbs of up to 400-500 g/year. The option of NRTI-sparing regimes is also available.

→

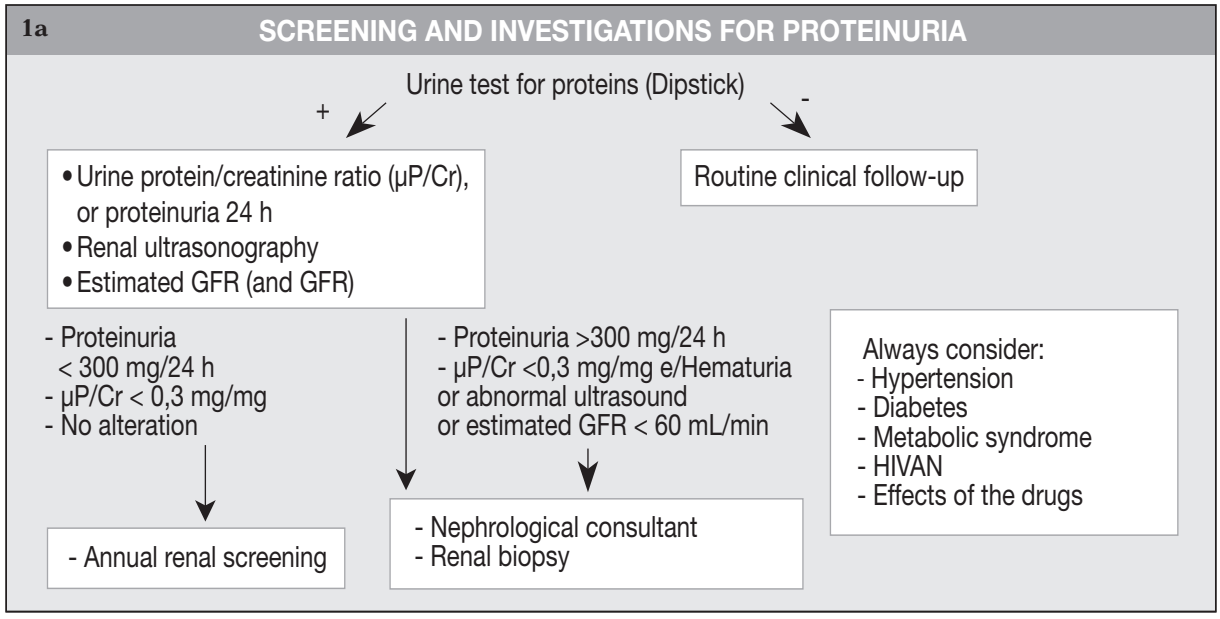
Prevention	*Management*
A correct diet and physical activity can reduce the accumulation of visceral fat and lead to improvement in insulin sensitivity and blood lipids, especially in obesity associated with lipo-hypertrophy. This intervention may, however, exacerbate subcutaneous lipo-atrophy.	Replace d4T or ZDV with abacavir (ABC) or tenofovir (TDF). The potential risk of toxicity linked with the use of these drugs must be taken into consideration. Avoid use of stavudine (d4T) and of zidovudine (ZDV, AZT), or switch to other drugs as prevention. Consider Nucleoside Reverse Transcriptase Inhibitors (NRTI)-sparing regimens. Using these regimes may be associated with an increase risk of dyslipidaemia. There are no antiretroviral therapy switch strategies with proven efficacy in the treatment of lipo-hypertrophy. Surgical intervention to correct facial lipo-atrophy is not aesthetic surgery but repair of an iatrogenic injury. Indeed, these have a positive effect on the quality of life and on depression, reducing the stigma of HIV disclosure and infection "revealed" by recognition of the lipo-dystrophic phenomenon, and is a potential intervention to support adherence to antiretroviral therapy. The surgical approach may be undertaken either by autotransplant of adipose tissue (lipo-filling) or by treatment with synthetic fillers (re-absorbable or not), in patients without adipose tissue for use as a donor site [BI]. The re-absorbable synthetic fillers are preferable in patients with less severe lipo-atrophy and under 50 years of age, while non re-absorbable synthetic fillers are preferred in cases of more severe lipo-atrophy in those over 50 years old [BIII]. The use of synthetic fillers is not recommended in the treatment of non facial lipo-atrophy. The use of medical therapies to improve lipo-atrophy has produced conflicting results. In particular, the use of thiazolidinediones such as rosiglitazone and pioglitazone did not result in a significant increase of adipose tissue. Use of rosiglitazone can cause blood lipid elevations and an increased risk of coronary heart disease. Several drugs have been used to treat lipo-hypertrophy. Growth hormone reduces visceral adipose tissue but may exacerbate subcutaneous lipo-atrophy and insulin resistance. Tesamorelin (growth hormone release factor), currently not authorized in Europe, has been shown to be efficacious in reducing the volume of visceral adipose tissue. Metformin reduces visceral adipose tissue in insulin resistant patients but may exacerbate subcutaneous lipo-atrophy. Surgical intervention to correct lipo-hypertrophy may be considered for removal of localised lipomas and to correct buffalo hump although the duration of the effect is variable [BIII].

Prevention and management of patients at high risk of kidney disease

Prevention	*Management*
Assessment of glomerular function is performed with prediction algorithms which include serum creatinine level, age, sex, ethnic origin and anthropometric measurements. Calculation of creatinine clearance is necessary, as the serum creatinine value depends to a variable extent on extrarenal factors; further, the correlation between creatinine and glomerular filtratation is not linear.	In cases of Fanconi syndrome in tenofovir-treated patients, tenofovir must be discontinued immediately. In patients with estimated glomerular filtrate <50 mL/min dose adjustments should be performed where necessary. The need for treatment modification should be assessed every time GFR is below 60 ml/min and/or in the case of observation of proteinuria/ microhematuria.

→

Prevention	*Management*
Measurement urine over 24 hours, while more tim-consuming, is more accurate and certainly preferable to use of the Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG), EPI-CKD formulae. Given the close connection between renal damage and cardiac damage, cardiovascular prevention interventions, with particular reference to hypertensive disease, appear efficacious in the prevention of kidney disease as well.	In these cases, risk assessment for renal dysfunction is indicated, discontinue or change drug doses where indicated, and consider ultrasonography of the kidneys; in the case of hematuria, irrespective of the degree of proteinuria, consult a specialist nephrologist.



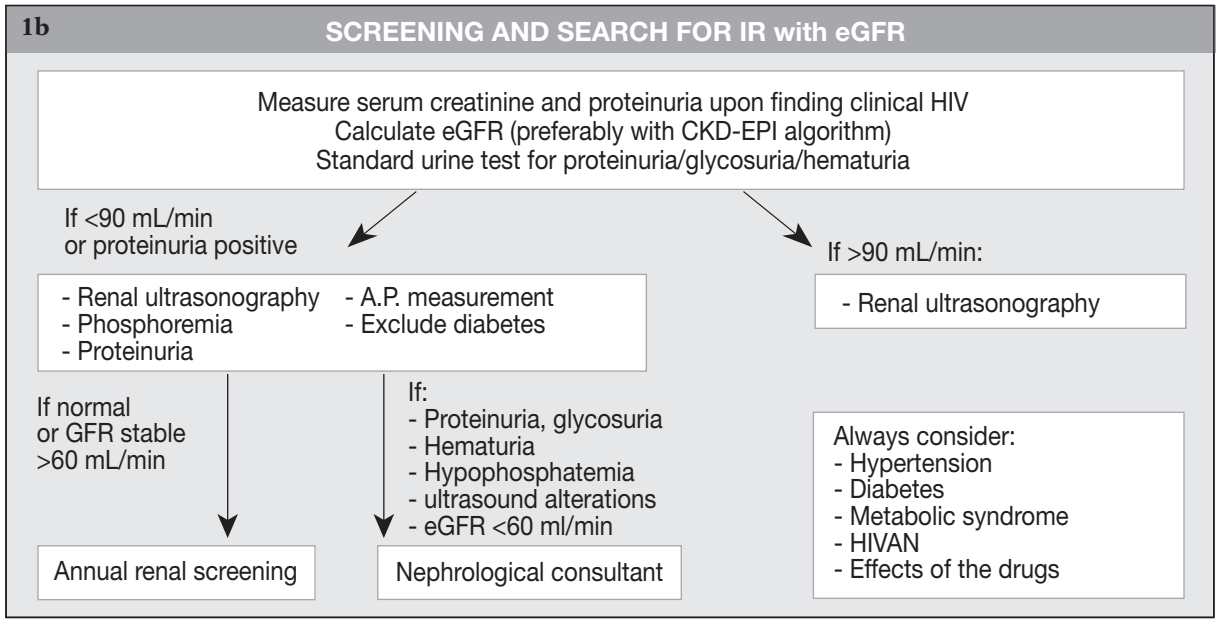


FIGURE 1 - *Clinical management of renal failure (1a) and proteinuria (1b).*

HIV-associated neuro-cognitive disorders

The clinical outcome and quality of life of people with HIV infection can be profoundly influenced by the presence of neuro-cognitive and/or psychiatric disorders, whether these are the consequence of HIV damage to the central nervous system (CNS) - defined in this case as *HIV-associated neuro-cognitive disorders* (HAND) , attributable to other causes, or to the combination of the two.

HIV does not infect neurons directly, but the infection and consequent activation of CNS macrophages, the target cells in this tissue, can trigger a cascade of events, including the production of inflammatory, neurotoxic molecules leading to neuron dysfunction, degeneration and death.

The clinical equivalent of these events is represented by a neurocognitive disorder which, in more severe forms, manifests with a state of dementia (HAD, *HIV-associated dementia*). A classification of HAND was recently proposed on the basis of the severity of the deficit, as established by neuropsychological examination.

TABLE 22 - *Classification of HIV-associated neurocognitive disorders (HAND).*

	Alteration in ≥2 cognitive areas documented by np exam	*Interference with daily life*
Asymptomatic Neurocognitive Impairment (ANI)	Present	No
Mild Neurocognitive Deficit (MND)	Present	Mild
HIV-associated dementia (HAD)	Present	Severe

HAND: HIV-associated - Disorders; ANI: Asymptomatic Neurocognitive Impairment; MND: Mild Neurocognitive Disorder; HAD: HIV-Associated Dementia; NP Exam: Neuropsychological Examination

While the incidence of HAD fell after the introduction of combination antiretroviral therapy (cART), the general prevalence of neuro-cognitive disorders rose, likely due the increase over time of incident cases and the longer survival of HIV-infected individuals, and now affects 25%-50% of patients. HAND is associated with several risk factors, including:

- A CD4+ nadir <200 cells/μL;
- Age over 50 years;
- Co-infection with HCV, diabetes or insulin resistance.

HIV-infected patients have a high prevalence of a number of conditions/comorbidities that are independently associated with neurocognitive disorders *which may contribute to or totally explain the cognitive deficit, and confound a diagnosis of HAND*:

- Depression;
- Anxiety disturbances;
- Psychoses and other psychiatric disorders;
- Vascular and ischemic dementia;
- Alzheimer's disease;
- Opportunistic infections or CNS neoplasia;
- Metabolic encephalopathies;
- Hepatic cirrhosis;
- Co-infection with HCV;
- Current or previous history of drug abuse (cocaine, methamphetamine, opiates);
- Abuse of psychiatric drugs;
- Alcoholism;
- Prior concussive cranial trauma.

Diagnosis of HIV-associated neurocognitive disorders (HAND)

The diagnostic procedures recommended for the management of the patient with or at risk of HAND are reported below.

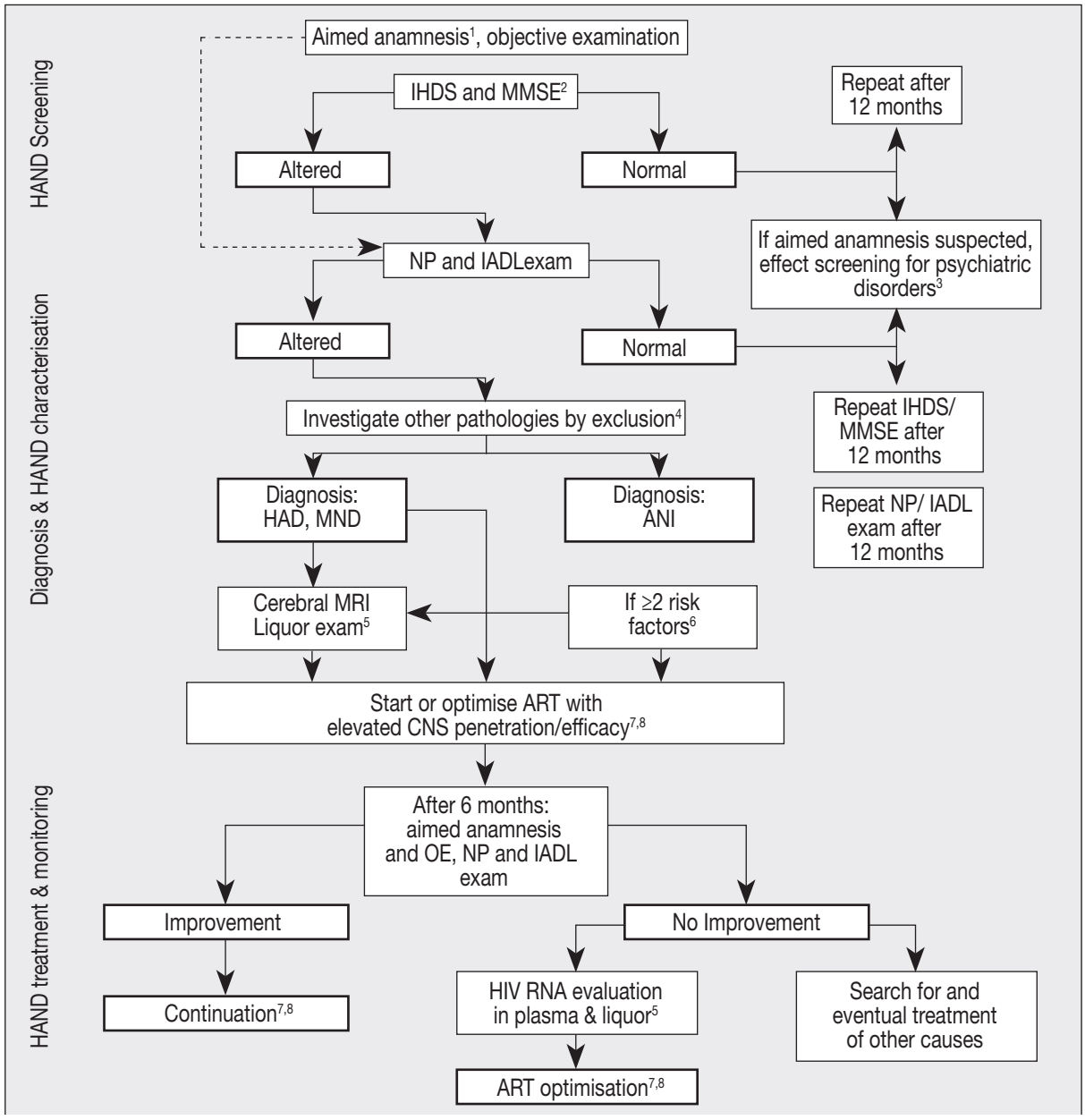


FIGURE 2 - *Diagnostic algorithm for the diagnosis and treatment of HIV-associated neurocognitive disorders (HAND).* Abbreviation legend - IHDS: *International HIV Dementia Scale*; MMSE: *Mini Mental State Examination*; IADL: *Instrumental Activities of Daily Living*; NP Exam: Neuropsychological Examination; MRI: Magnetic Resonance Imaging of the brain with contrast media. Notes on the algorithm: [1]To highlight difficulties in the execution of one or more of the following functions: plan and execute complex tasks; perform simple, timed, cognitive functions; maintain usual levels of attention; have good temporal-spatial orientation; maintain behaviour suitable to environmental circumstances; have good prospective memory or memory of activities or future plans; and to highlight shades of possible psychiatric symptomatology (e.g. symptoms of depression or anxiety). [2]Patients with evident and/or documented neurocognitive alterations do not require screening tests and are direct candidates for NP exam. To enhance the diagnostic sensitivity of the MMSE some experts propose raising the classic cut-off from 24/30 to 28/30. [3]In patients with symptoms not explained by neurocognitive alterations, specialist consultation is indicated for the diagnosis and treatment of possible psychiatric or psychological disorders. [4]Include neurological examination and blood tests to exclude conditions/co-morbidities associated with non-HAND neuro-cognitive disorders. [5]Risk factors: CD4+ nadir <200 cells/μL, age >50 years, HCV-Ab positivity, diabetes or insulin resistance. [6]Examinations aims to distinguish HAND and exclude other pathologies. The CSF test is indicated principally to study HIV-RNA level (concomitant with evaluation of plasma viremia) and of drug resistance. [7]To define drugs with elevated penetration and efficacy in the CNS, the use of *Central nervous system Penetration Effectiveness* - CPE Score (*Letendre S et al.*, CROI 2010) is recommended [see below].

TABLE 23 - *Diagnostic route to diagnosis of HIV associated neurocognitive disorders (HAND).*

Level	*Examination(S)*	*Objective(S)*	*Population*
1a	Targeted history-taking*, neurological examination	Identification of patients with possible neurocognitive or psychiatric disorders	All [AIII]
1b	IHDS, MMSE	Identification of patients with possible neurocognitive disorders.	All [AIII] or, where not practicable in all, at least in patients with 1 or more risk factors (Figure 1, note 5)
2a	Neuropsychological examination	Diagnosis of neurocognitive impairment and definition of severity.	Patients with suggestive clinical history [AII]; patients with IHDS ≤10 [AII] or MMSE <28** [BII]
2b	IADL questionnaire	Evaluation of functional impact Diagnosis of HAND severity	Patients with altered NP exam [AII]
2c	Specific questionnaire	Screening for depression and other psychiatric disorders	Patients with symptoms emerging at anamnesis, but NP exam within the norm [AII]
2d	Laboratory and instrumental tests	Exclude confounding disorders	Patients with altered NP exam [AII]
3a	Neurological examination	Exclude confounding disorders Diagnosis of HAND severity	Patients with altered NP exam [AII]
3b	MRI of the brain	Exclude confounding disorders Search for HAND compatible signs	Patients with HAD or MND [AII] Patients with ANI and ≥2 risk factors [BII]
3c	Examination of cerebrospinal fluid (CSF) specimen	Exclude confounding disorders HIV-RNA, GRT	Patients with HAD [AII] or MND [BII] Patients with ANI and ≥2 risk factors [BII]

GRT: Genotypic Resistance Test. *See note 1 above. **See note 2 above.

TABLE 24 - *Antiretroviral therapy in patients with mild neuro-cognitive disorders (MND) or HIV-associated dementia (HAD).*

	Clinical scenario and possible biological basis	*ARV Therapy**
Not on ARV therapy, MND/HAD	Productive infection of CNS	ARV therapy with 3 drugs, all with elevated penetration and efficacy in the CNS, also taking into account GRT in plasma and, if available, in CSF [AII]
On ARV therapy with therapeutic failure, MND/HAD	a) HIV RNA detectable in CSF with GRT comparable or different to plasma: productive infection of CNS due to to high viral replication in the CNS and/or resistance in the CNS and/or poor penetration/ efficacy of ART in CNS. b) HIV-RNA not detectable in CSF: possible low-level HIV replication in CSF or presence of chronic CNS damage	Modification of ARV therapy on the basis of the GRT on plasma (a, b) and on CSF (a), using more effective or at least equivalent o current therapy in terms of CNS penetration and efficacy.
On ARV therapy with viremia suppressed, MND/HAD	a) HIV-RNA detectable in CSF: productive infection of CNS due to compartmentalised viral replication and/or resistance in CSF and/or poor penetration/ efficacy of ART in CNS. b) HIV-RNA not measurable in CSF: possible low-level HIV replication or presence of chronic damage to CNS.	Modification of ARV therapy on the basis of the GRT on CSF and previous resistance tests on plasma, with preference for agents with elevated CNS penetration and efficacy (a) [AII]. Strengthening therapy by addition of one or more drugs with elevated CNS penetration and efficacy (a, b) [BIII].

*For drugs with elevated CNS penetration and efficacy, refer to Table 3 on the CPE score (see full version of the Guidelines), in which the drugs with most elevated penetration and efficacy are assigned a higher score.

Prevention of symptomatic HIV-associated neuro-cognitive disorders (HAND) (MND, HAD)

In the absence of MND or HAD it is important to identify the patients most at risk of developing symptomatic neuro-cognitive impairment in the future and to employ effective strategies for its' prevention.

In both patients with ANI, and patients without neuro-cognitive alterations, but with risk factors (CD4+ nadir <200 cells/μL, age >50 years, co-infection with HCV, diabetes or insulin resistance), careful neuro-cognitive monitoring is indicated (with NP and IADL exam every 12 months to evaluate eventual evolution towards MND) [AII]; the use of drugs with elevated CNS penetration and efficacy both in cases of with ≥2 risk factors for HAND development [AII], and in patients with no compromise and ≥2 risk factors is suggested[CIII].

TABLE 25 - *Monitoring the efficacy of antiretroviral therapy in HIV-Associated neuro-cognitive disorders (HAND).*

Level	*Scenario*	*Objective*	*Examinations*
1	Starting or changing cART, HAND	Initial evaluation of the efficacy of the (new) therapy on the neuro-cognitive impairment	After 6 months: NP exam [AII]
2°	cART monitoring: HAND with recovery of neuro-cognitive impairment	Monitor the efficacy of cART on the neuro-cognitive impairment	Every 12 months: NP exam [AII]
2b	cART monitoring: HAND with no recovery or worsening of neuro-cognitive impairment	Search for virological escape in the CNS Exclusion of other causes of neuro-cognitive impairment	Neurological examination [AII] MRI of the brain [AII] CSF examination (HAD and MND) and tests to exclude other disorders [AII], HIV RNA [AII], GRT [AII] After 6 months: NP exam [AII]

Tumours

Treatment for HIV-associated tumours is very complex and must be the product of a strategic and operative agreement between the oncologist and the infectious disease specialist.

This section is intended to focus only on certain aspects of this complex problem, mainly addressing the general principles of timing, choice and management of antiretroviral therapy in the HIV patient with malignancies.

Thus, this discussion must not be considered an exhaustive review of the complex issue of tumour management in the HIV-infected patient, a scenario which requires specific study and recommendations in clinical, diagnostic and therapeutic domains.

HIV-positive patients must regularly undergo screening for solid cancers, in particular for breast cancer, colorectal neoplasia and prostate carcinoma, whose cost-efficacy is largely documented in the general population [AI].

Initiation of HAART is, in general, recommended concomitant to the anti-neoplastic treatment [AII], with the possible exception of patients with non-AIDS defining cancers, elevated CD4+ levels, and possible drug interactions associated with severe with toxicity [BIII]. HAART is recommended in all patients treated with highly immunosuppressive therapies.

In candidate patients for concomitant treatment with HAART and chemotherapy (CT), consideration of possible drug-drug interactions and cumulative toxicity must guide and orient the choice of antiretroviral therapy.

The potential interactions between antiretrovirals and chemotherapy should be considered before the a therapeutic regimen is chosen [AIII], with reference to the most up to date data in the literature (see http://www.hiv-druginteractions.org).

The use of antiretroviral TDM is recommended to check for interactions and accumulated toxicities [CIII].

INFECTIVE COMORBIDITY

Infection by hepatitis viruses

When to start antiretroviral therapy

Patients with hepatitis virus co-infection - Maintenance of CD4+ count over 500 cells/μL and HIV viral suppression are recommended [BII].

Patients with HCV co-infection - With a CD4+ count >500 cells/μl, starting antiretroviral therapy is highly recommended [AII]. In patients with indications for anti-HCV therapy with interferon and ribavirin and with CD4+ <500 cells/μL or with unstable HIV disease (indicated by HIV-RNA >100.000 copies/mL and/or decline of the CD4+ >100 cells/ L in the last year) anti-HCV therapy should be preceded by the initiation of antiretroviral therapy[AIII].

Patients with indication for anti-HBV therapy - In patients with indications for treatment of chronic hepatitis B, starting antiretroviral therapy is recommended independently of the CD4+ count and of the other parameters, administering tenofovir in combination with lamivudine or emtricitabine and a third drug or, alternatively, tenofovir with another nucleoside active on HBV (telbivudine or entecavir) in addition to another two antiretrovirals [AII].

TABLE 26 - *Antiretroviral therapy in HIV-infected individuals with coinfections with viral infections (HBV and HCV).*

	Coinfection with HCV	*Coinfection with HBV*	*Cirrhosis*
TDM	-	-	Use in patients with decompensated cirrhosis
When to start	Recommended at a CD4 level <500 cell/mm^3		
What to start with (NRTI backbone)	Avoid didanosine and stavudine; abacavir only after HLA-B*5701; avoid zidovudine if the patient is candidate to Peg-IFN+RBV	Use tenofovir+XTC; do not use XTC as only drugs active on HBV	-
What to start to (third drug)	Avoid tipranavir and full-dose ritonavir; use nevirapine only as alternative		
	Use NNRTI or PI or Integrase inhibitor with a low impact on insulin resistance	No other indications	Saquinavir not indicated in decompensated cirrhosis; adjust dosing in Child-Pugh classification of Class B*; use TDM if Child-Pugh classification of Class C
Management of first failure and successive or alternative treatment strategies	-	Do not discontinue anti-HBV drugs if staging is >F2 according with METAVIR	-

*Caution and monitoring of side effects in the case of hepatic impairment (Child-Pugh >7 points) when efavirenz, lopinavir/r, raltegravir, maraviroc are used; in patients with severe hepatic impairment increasing levels of plasma concentration of efavirenz and maraviroc have been observed [BIII]. Use atazanavir at dosing of 300 mg daily (without ritonavir) in patients with cirrhosis and Child-Pugh score between 7 and 9 [BII]. In adults with mild hepatic impairment (Child-Pugh score 5-6 points) the recommended dosing of fosamprenavir is 700 mg BID with ritonavir 100 mg daily [BII]. In adults with moderate hepatic impairment (Child-Pugh score 7-9 points) the recommended dosing of fosamprenavir is 450 mg BID with ritonavir 100 mg daily

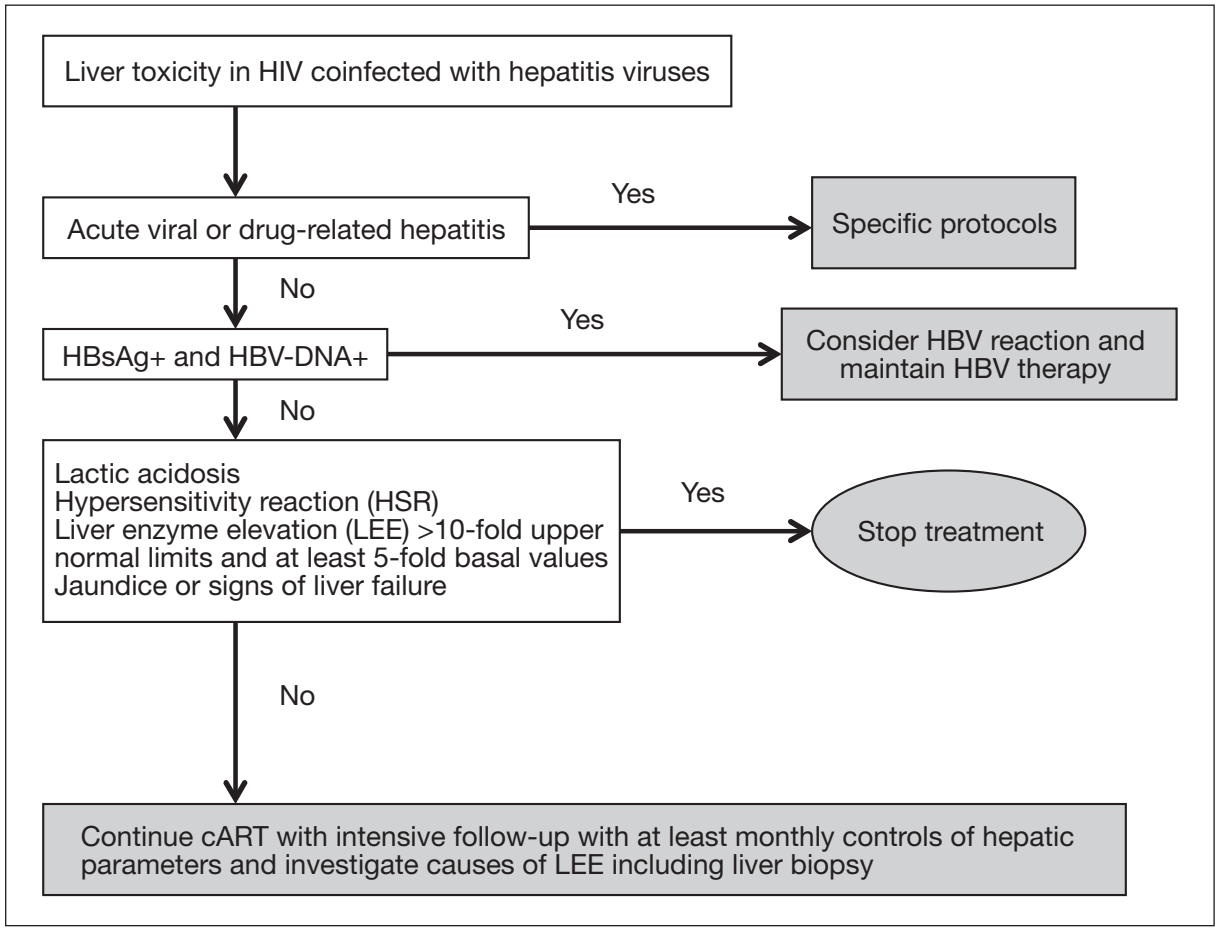


FIGURE 3 - *Management of liver toxicity in HIV-infected individuals treated with antiretrovirals.*

Tuberculosis

The critical passages regarding the use of combination antiretroviral therapy (cART) in subjects with tuberculosis are:

- Optimal timing of cART initiation with respect to the tuberculosis treatment.
- The selection of antiretroviral drugs to be administered with the tuberculosis therapy on the basis of assessment of potential pharmacokinetic interactions and possible cumulative toxicity.
- The risk of developing an immune reconstitution (inflammatory) syndrome (IRIS) after initiation of cART and its management.

TABLE 27 - *Principles of ARV management in HIV-infected patients with tuberculosis.*

	Recommendations	*Comments*
When to start	Strongly recommended to start cART within three months from the initiation of tuberculosis therapy, independently from CD4 count or plasma HIV-RNA levels	- In patients with CD4 <350 cell/mm3, is recommended to start cART as soon as possible after 2 weeks from the initiation of tuberculosis treatment, in order to evaluate potential adverse reactions to the tuberculosis drugs. - In patients with CD4 between 350 and 500 cell/mm3, an early starting of cART is recommended (between 2 weeks and 2 months from the initiation of tuberculosis treatment) - In patients with CD4 >500 cell/mm3, the optimal timing of cART initiation should be evaluated in the single case, on the basis of cost-effectiveness assessment.
What to start with	Use EFV+2NRTI as choice regimen to be combined with a rifampin-based tuberculosis regimen[BI]	The use of PI/r or PI, combined with rifampin is not indicated. Using PI/r or PI (except for unboosted saquinavir) is feasible if combined with rifabutine [BII]. All these combinations should be used in patients with resistance to NNRTIs or in the case in which NNRTIs are not tolerated.
Immune reconstitution syndrome (IRIS) after cART initiation	Delaying cART initiation after the first months from starting tuberculosis treatment, the incidence and severity of IRIS could be reduced. This strategy is not recommended in patients with CD4 <350 cell/mm^3 [AI]. Do not discontinue cART in case of IRIS [AII]	

Opportunistic Infections

TABLE 28 - *Initiation of antiretroviral therapy during acute opportunistic infection.*

Elements which must be considered include the degree of immuno-suppression, the availability of effective therapy for O.I.S, pharmacological interactions and cumulative toxicity, and the risk of iris
In the absence of obvious contraindications, early initiation of ART in the initial phases of an acute O.I.
Immediate initiation of ART is highly recommended in patients with opportunistic infections for which efficacious specific therapies are lacking, such as cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), localized cutaneous and mucosal Kaposi sarcoma (KS), multi-resistant herpes simplex infection.
In patients with PCP initiation of ART is highly recommended within 2 weeks of the diagnosis of PCP.
In O.I.s in which the risk of IRIS is higher (tuberculosis, cryptococcal meningitis, atypical micobacterial infections, CMV infection), delayed initiation of ART may be considered.

TABLE 29 - *Management of opportunistic infections during antiretroviral therapy.*

Opportunistic Infections	*Considerations*
<12 weeks of ART	- Administer anti-O.I. therapy - Continue ART [AIII] - Consider IRIS
>12 weeks of ART with virological suppression and immunological recovery	- Administer anti-O.I. therapy - Continue ART [AIII] - Consider IRIS Assess whether to modify or intensify ART in case of suboptimal recovery of CD4+ lymphocytes [CIII]
>12 weeks of ART with virological failure	- Perform resistance test [AI] - Administer anti-O.I. therapy - Modify ART [AI]

ANTIRETROVIRAL THERAPY IN PREGNANCY

General aspects of antiretroviral treatment during pregnancy

Many aspects of antiretroviral therapy in pregnancy are as yet unclear due to the difficulty of conducting randomized clinical studies in this setting and the difficulty of responding to particular clinical questions through controlled clinical or observational studies. In particular, there is no evidence to guide: the optimal timing antiretroviral treatment initiation in pregnancy for women who have no other indication for the treatment, which choice of drugs and regimens is safe to continue during the pregnancy, and what is the long-term impact of antiretroviral therapy during pregnancy on survival.

Approach to antiretroviral therapy in pregnancy

The recommended therapeutic approach is based on the combined administration of ante partum and intra partum maternal therapy and on antiretroviral prophylaxis in the newborn. This therapeutic schema should be applied to all pregnant women with HIV, independent of the CD4 and HIV-RNA values. Where, due to late access to treatment, the ante partum or intra partum therapy cannot be delivered, administration of the remaining components of the therapeutic schema is fundamental.

It is necessary to consider separately women with maternal indications for antiretroviral therapy and those whose sole indication is the prevention of vertical transmission.

Principal therapeutic scenarios

Pregnant women with maternal indication for antiretroviral treatment must receive a combination regimen of potency analogous to that recommended in non-pregnant women. If the woman is not yet undergoing treatment and there is indication for immediate treatment, it must be initiated as soon as possible. For women with no indication for antiretroviral therapy, the general recommendation is to administer, in all cases, a potent combination regimen, as combination regimens have been found to be the most effective in preventing vertical transmission.

Independent of the individual indication for antiretroviral therapy in pregnancy (presence or otherwise of the maternal indication for treatment in addition to prevention of vertical transmission), the use of antiretroviral mono-therapy in pregnancy should be considered inadequate due to its suboptimal antiviral efficacy, the higher risk of development of resistance, and the greater efficacy of the combined therapy in preventing vertical transmission.

Pregnancy is characterized by significant physiological changes operating at different levels on absorption, distribution, metabolism and elimination of drugs. Reduced plasma levels of drugs in pregnancy have been reported by diverse authors, especially in the third trimester, most frequently protease inhibitors, which show greater variability than NRTI and NNRTI.

Monitoring plasmatic drug levels

In general, plasmatic drug level monitoring is not recommended (TDM) in all pregnant women with HIV undergoing treatment, but should be considered in particular situations (e.g.: pathologies or concomitant treatments which can significantly interfere with the metabolism, drugs or regimens particularly those for which there is no available data during pregnancy, toxicity or inefficacy of unclear cause, need to precisely define the levels relative to the presence of resistance, etc.). For the management of these problems, increasingly interesting and growing in complexity, please refer to the specific section dedicated to Pharmacological Monitoring and Interactions.

Virological monitoring during pregnancy: viral load and resistance

Virological objectives of antiretroviral treatment in pregnancy

Viral load monitoring in pregnancy is of particular relevance as the maternal viral load is an independent determinant of vertical transmission.

It is thus particularly important to maintain the viral load undetectable in women at the beginning of the pregnancy and to achieve viral suppression of HIV as rapidly as possible to undetectable levels in women commencing treatment during pregnancy.

Viral load monitoring may be performed every two-three months in women on stable therapy and with undetectable HIV at baseline, while in women commencing treatment or requiring modification during pregnancy closer monitoring of response to treatment is advised.
An HIV-RNA assessment is recommended in all women at about week 34-36 of gestation.

Therapeutic failure
In the presence of therapeutic or virological failure, it is necessary to rapidly modify the treatment in order to guarantee the lowest possible levels of viral load at the time of delivery.
To his end, a resistance test to guide the choice of treatment is highly recommended.

Performance of resistance testing
The use of the resistance assay during pregnancy, follows the general directives regarding adults a resistance test is recommended in all women not yet on treatment and in all those undergoing treatment with a confirmed detectable RNA.
The test must be ordered in a timely manner, and optimal period for delineation of resistances and choice the treatment in pregnancy is the pre-conception period.

Antiretroviral therapy in women already undergoing treatment at conception
Ideally, the regimen at conception should have been selected in the pre-conception period according to criteria which assure safe usage in pregnancy, so that modification or interruption is not required in the early weeks of gestation.
In prescribing potentially teratogen drugs (e.g. efavirenz) to women of reproductive age or other regimens or drugs characterised by additional risk of toxicity in pregnancy (e.g. lactic acidosis, hepatotoxicity, diabetes), it is necessary to consider the possibility of an unplanned pregnancy and individually assess the risk/benefit of treatment relative to the risk of unplanned pregnancy.
In women undergoing antiretroviral treatment with unplanned pregnancy, the regimen must be re-assessed as soon as possible in order to determine its safety for use in pregnancy.

Antiretroviral treatment in women who have never received antiretrovirals prior to pregnancy
Choice of the treatment regimen
Where there is a maternal indication for treatment, it must commence as soon as possible, also in the first trimester, using a potent regime of a combination of drugs which has the best evidence for safety in pregnancy.

Where the indication for treatment is solely for prophylaxis of vertical transmission, it is possible to consider and discuss with the patient initiation of treatment after the first trimester, but it is necessary to consider that in the absence of treatment there is a risk of *ante partum* transmission.

Timing of starting treatment
It is not possible to recommend, on the basis of the available evidence, an optimal timing for starting of the antiretroviral treatment in pregnancy for women with no personal indication for treatment [9], but the trimester for initiation of the treatment must guarantee a therapy duration sufficient to achieve complete viral suppression in the final phases of the pregnancy, also considering the possibility that the duration of the pregnancy may be reduced by the risk of pre-term birth.

Potency of the regimen
In all women, including those with no personal indication for treatment, the potency of the regime must be adequate to achieve complete viral suppression, and in general, combination regimens must used at the same potency of those recommended for the treatment of all adults. In the case of women with viral loads below 1000 copies/mL in the absence of treatment, controversy remains as to whether regimens of lesser potency than those used for treatment of adults are to be recommended.

Interruption of treatment
In the case of interruption of antiretroviral treatment during pregnancy, treatment interruption must be immediate and simultaneous for all drugs in cases of severe and life threatening toxicity or grave hyperemesis. In case of elective interruption, in order to prevent the selection of re-

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sistant strains, if agents with a long half-life are part of the regimen (e.g. NNRTI, non nucleoside analogues), it is strongly recommended the sequential discontinuation of drugs with long half lives first, with continued administration of other regimen components for a period of time sufficient to guarantee triple antiretroviral coverage as NNRTI levels diminish.

Continued administration of the other drugs for at least 7 days may be considered sufficient, but there is notable variability in the time at which the NNRTIs become undetectable in plasma after discontinuation.
Recent Italian data, while limited to a number of vertical transmission cases and not exclusively involving HAART therapies but including monotherapy (10.6%) and dual therapy (20.0%), suggest that interruptions of treatment in pregnancy may constitute a significant risk factor for mother-to-child HIV transmission.

POST-EXPOSURE PROPHYLAXIS

Indications for post-exposure prophylaxis

- PEP must be initiated as soon as possible after exposure, preferably within 1-4 hours, and no later than 48 hours [AII].
- Exposed subjects who have initiated PEP must be evaluated by an expert within 48-72 hours of treatment initiation [AIII].
- In those cases where the serostatus of the source patient is unknown and the source patient is available, an targeted epidemiological investigation should be conduced and a serological test performed, once consent has been obtained; the result must be rapidly available, and where available rapid tests should be used[AIII].
- Where serological testing is not possible in the time available, commencement of treatment is recommended with a new visit planned to re-evaluate transmission risk, once source-patient test results have been obtained [AIII].
- An exposure source patient who refuses consent to testing must be considered HIV-infected [AIII].
- Tests based on detection of antigens and antibodies are preferable. Use to bio-molecular techniques is not indicated for the purpose of ascertainment of infection [AII].
- Performance of ad hoc tests to determine resistance to the ARVs is not recommended [AIII].
- During initial counseling of the exposed subject, the risks connected with the specific exposure must be explained in order to facilitate correct perception of the probability of infection and facilitate decision-making on PEP uptake (*Tables 1* and *2*) [AIII].

TABLE 30 - *Recommendations for offering PEP.*

a) OCCUPATIONAL EXPOSURE	
Exposure Mode	*Source Patient*
	HIV+* or HIV negative but with history or current pathology indicative of very recent at risk exposure (e.g. acute viral hepatitis, IST, endocarditis of right heart) or refusing to consent to serology tests for HIV
Conjunctival contamination with blood or CSF Exposure to material with elevated viral concentration (e.g. cultures, concentrated suspensions of virus) in any modality.	HIV+*
*The risk is significantly reduced if the source is on ARV therapy with consistently undetectable viral loads in recent months. In situations other than those indicated, PEP may be considered by an expert on the basis of careful assessment of the risk taking into account the efficiency of transmission connected with the exposure modality and the contagiousness of the source.	

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b) NON OCCUPATIONAL EXPOSURE	
Exposure Mode	*Source Patient*
Anal, vaginal, oral sex Receptive with internal ejaculation	HIV+* or HIV negative but with history or current pathology indicative of very recent at risk exposure (e.g. acute viral hepatitis, IST, endocarditis of right heart) or Serology for HIV not known in subject with high risk behaviour or in the case of rape/sexual violence
Insertive anal or vaginal sex Without protection or inefficacious protection	HIV+*
Receptive anal, vaginal, oral sex No internal ejaculation no protection	HIV+* or in the case of rape/sexual violence
Exchange of syringe or other material in common use for narcotic consumption	Independent of the serological state of the source
*The risk is significantly reduced if the source is on ARV therapy with consistently undetectable viral loads in recent months; risk is augmented if trauma is verified (e.g. traumatic injury after rape), if there is a presence of blood or current STI especially if with ulcerating disease. In situations other than those indicated, PEP may be considered by an expert on the basis of careful assessment of the risk taking into account the efficiency of transmission connected with the exposure modality and the contagiousness of the source.	

Prophylaxis regimes

- PEP must be composed of a three drug combination regime [AIII].
- PEP must be continued for 28 days [AIII].
- In the case of an HIV positive source, the choice of drugs must be guided by the resistance profile by genotyping, if available, or from the chart review [AII].
- The medical history of the exposed and eventual interactions with other drugs must be considered in the choice of the drugs [AIII].
- Any combination of ARV drugs approved for the treatment of patients with HIV infection may be used for PEP, with the same contraindications, including new drugs which become available in the future [AIII].
- At this time nevirapine is the sole drug whose use is not recommended, in the presence of alternatives, due to severe toxicity in immune competent subjects. The use of stavudine and of abacavir should be reserved solely for those cases without valid alternatives, due to possible serious reactions [AII].
- Pregnancy is not an absolute criterion for exclusion from PEP; the use of efavirenz is not recommended (possible teratogenicity), stavudine and didanosine (lactic acidosis), indinavir (hyperbilirubinaemia as birth approaches) [AII].

TABLE 31 - *Antiretroviral regimens recommended and alternative for PEP.*

Regimes	
Recommended regime	2 N(t)RTI + PI/r
Alternative regime*	2 N(t)RTI + INI (Integrase Inhibitor)
*especially in cases of post coital contraception	

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Institutional Responsibility*:** Barbara Ensoli (*Istituto Superiore di Sanità, National AIDS Centre, Rome*); Mauro Moroni (*University of Milan, Milan*); ***General Coordinators: Adriano Lazzarin (*San Raffaele Scientific Institute, Milan*), Evangelista Sagnelli (*University of Naples, Naples*); ***Executive Committee:*** Andrea Antinori, (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*), Giampiero Carosi (*University of Brescia, Brescia*), Simone Marcotullio (*Nadir Onlus Foundation, Rome*); Francesco Mazzotta (*S.M. Annunziata Hospital, Florence*); Stefano Vella (*Istituto Superiore di Sanità, Department of Therapeutic Research and Medicine Evaluation, Rome*)

Members
Adriana Ammassari (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Giorgio Antonucci, (*National Institute for Infectious Diseases L. Spallanzani IRCCS, Rome*); Massimo Andreoni (*University of Tor Vergata, Rome*); Gioacchino Angarano (*University of Bari, Bari*); Orlando Armignacco (*Belcolle Hospital, Viterbo*); Sergio Babudieri (*University of Sassari, Sassari*); Franco Baldelli (*University of Perugia, Perugia*); Teresa Bini (*San Paolo Hospital, University of Milan, Milan*), Paolo Bonfanti (*L. Sacco Hospital, Milan*); Stefano Bonora (*University of, Turin, Turin*); Marco Borderi (*Sant'Orsola Malpighi Hospital, Bologna*); Raffaele Bruno (*San Matteo Hospital, University of Pavia, Pavia*); Raffaella Bucciardini (*Istituto Superiore di Sanità, Department of Therapeutic Research and Medicine Evaluation, Rome*); Antonella Castagna (*San Raffaele Scientific Institute, Milan*); Anna Maria Cattelan (*Santa Maria della Misericordia Hospital,* Rovigo); Roberto Cauda (*Catholic University, Rome*); Alessandra Cerioli (*Italian League for the War against AIDS, LILA, Bologna*); Antonio Chirianni (*Cotugno Hospital, Naples*); Antonella Cingolani (*Catholic University, Rome*); Paola Cinque (*San Raffaele Scientific Institute,* Milan); Antonella d'Arminio Monforte (*San Paolo Hospital, University of Milan, Milan*); Gabriella De Carli (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Andrea De Luca (*Catholic University, Rome; University Hospital, Siena*); Giovanni Di Perri (*University of Turin, Turin*); Massimo Di Pietro (*S.M. Annunziata Hospital, Florence*); Issa El Hamad (*Civil Hospitals, Brescia*); Mariangela Errico (*NPS Italia NGO, Naples*); Enrico Ferrazzi (*University of Milan*, Milan); Marco Floridia (*Istituto Superiore di Sanità, Department of Therapeutic Research and Medicine Evaluation, Rome*); Eugenia Gabrielli, *L. Sacco Hospital Trust, Milan*); Massimo Galli (*University of Milan,* Milan); Carlo Giaquinto (*Padua Hospital, Padua*); Enrico Girardi (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Andrea Gori (*San Gerardo Hospital, Milan-Bicocca University, Monza*); Paolo Grossi (*Insubria University, Varese*); Giovanni Guaraldi (*University of Modena & Reggio Emilia, Modena*); Giuseppina Liuzzi (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Sergio Lo Caputo (*S.M. Annunziata Hospital, Florence*); Franco Maggiolo (*Ospedali Riuniti of Bergamo, Bergamo*); Marina Malena (*Community Medical Centre ULSS 20, Verona);* Renato Maserati (*San Matteo Hospital, University of Pavia, Pavia*); Claudio Mastroianni (S.M. Goretti Hospital, *La Sapienza University, Polo Pontino, Latina*); Alberto Matteelli (*University of Brescia, Brescia*); Aldo Morrone (*National Migrants & Poverty Institute,* Rome); Rita Murri (*Catholic University, Rome*); Cristina Mussini (*University of Modena & Reggio Emilia, Modena*); Paola Nasta (*Civil Hospitals, Brescia*); Massimo Oldrini (*Italian League for the War against AIDS, Milan*); Fabrizio Oleari (*Ministry of Health, Rome*); Giovanna Orlando (*L. Sacco Hospital, Milan*); Giorgio Palù (University of *Padua, Padua*); Raffaele Pempinello (*Cotugno Hospital, Naples*); Carlo-Federico Perno (*University of Tor Vergata, Rome*); Tullio Prestileo (*Civic Hospital, Palermo*); Maria Grazia Pompa (*Ministry of Health Rome*); Massimo Puoti (Niguarda Hospital, Milan); Vincenzo Puro (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Laura Rancilio (*Italian Caritas, Milan*); Guido Rasi (*Italian Medicines Agency, AIFA, Rome*); Giuliano Rizzardini (*L. Sacco Hospital, Milan*); Valeria Maria Savasi (*University of Milan, Milan*); Liana Signorini (*Civil Hospitals, Brescia*); Laura Sighinolfi (*S. Anna Hospital, Ferrara*); Maria Stagnitta (*National Reception Communities Coordination Committee, Florence*); Fabrizio Starace (*Department of Psychiatry, Policlinico of Modena*); Giulio Starnini (*Belcolle*

Hospital, Viterbo); Gaetana Sterrantino (*Careggi Hospital, Florence*); Fredy Suter (*Ospedali Riuniti of Bergamo, Bergamo*); Enrica Tamburrini (*Catholic University, Rome*), Giuseppe Tambussi (*San Raffaele Scientific Institute, Milan*); Marcello Tavio (*Ancona Hospital, Ancona*); Carlo Torti (*University of Brescia, Brescia*); Valerio Tozzi (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Maria Paola Trotta (*National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome*); Emanuela Vaccher (*Oncological Reference Centre, CRO, Aviano-PN*); Alessandra Viganò (*L. Sacco Hospital, Milan*); Raffaele Visintini (*San Raffaele Scientific Institute, Milan*); Vincenzo Vullo (*La Sapienza University, Rome*); Gian Vincenzo Zuccotti (*University of Milan, Milan*).

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