Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. Update 2011

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INTRODUCTION (Table 1)

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 available at the website: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1301_allegato.pdf.

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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.

As in the previously released version, it was decided not to discuss *in toto* 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, reference should be made to 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.

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 obtained from at least one controlled, randomized study with sufficient power or from a 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 competence 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 build rapport and 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 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, according with the official Consensus Document on the Policy of Offering and Performing HIV Testing in Italy.
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). Real Time polymerase chain reaction (PCR) should be considered the standard of care and its employment is strongly recommended [AI].
The main 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 clinicians 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 [AII]. 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 (Tables 2-4)

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 for MND or HAD. Could be considered for ANI	[AII] [BII]
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+: ≤500 cells/µL	Highly recommended	[AII]
Asymptomatic	CD4+: >350 cells/µL	Highly recommended	[AI]
Asymptomatic	CD4+: >500 cells/µL	*Highly recommended* in the presence of: a) HIV-RNA >100.000 copies/mL b) decrease of CD4+ >100 cells/µL per year c) age >50 years d) chronic HCV hepatitis	[AII]
		Moderately recommended in the case of highly motivated patients, considering the reduction of risk of HIV transmission	[BII]
		Moderately recommended in the case ofelevated cardiovascular risk:diabetes mellitus, or previous cardiovascular event, or elevated risk (>20%) in the next 10 years (estimate with *Framingham* algorithm)	[BIII]
*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 initiation of antiretroviral therapy*	*Strength/evidence (referred to the timing of ommencement of ARV therapy)*
- Multifocal progressive leukoencephalopathy - HIV encephalopathy -bWasting syndrome - Enteritis from *Cryptosporidium* or *Microsporidia*	Immediate initiation highly recommended	[AII]
Pneumonia from *P. jiroveci*	Highly recommended initiation within 2 weeks of diagnosis	[AI]
Tuberculosis	ART initiation *highly recommended* during anti-tubercular therapy - CD4 <50 cells/mm^3: initiation recommended at 2 weeks from starting of anti-tubercular therapy - CD4 50-500 cells/mm^3: initiation recommended within 2 weeks and 2 months of anti-tubercular therapy - CD5 >500 cells/mm^3: initiation to be established on individual basis, according with cost-benefit evaluation	[AI] [AI] [AI] [BII]
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 (Tables 5-9)

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

a) 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).
b) Factors regarding the overall clinical status, genetic factors, and characteristics of the patient including:
   - Comorbidities (cardiovascular disease, hepatic, renal disease, neurocognitive 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, advisable for all patients, is mandatory 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 report, 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	TDF/FTC* [AI]	Superior to ZDV/3TC; co-formulated; QD.
Choice	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**[AI]***	Non-inferior to ZDV/3TC; non-inferior to TDF/FTC in presence of viremia equal or lower than 100,000 copies/mL; inferior to TDF/FTC in presence of viremia greater than 100,000 copies/mL when combined with ATV/r or EFV, but not 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, and used with caution in patients with osteoporosis.
**Abacavir can only be used in HLA-B*5701 negative patients (screening recommended [AI]) and clinical HSR surveillance must be maintained in these patients; some studies have shown an increased risk of cardiovascular disease, even though two recent meta-analyses have not confirmed these results; do not initiate concomitant treatment with nevirapine due to augmented risk of hypersensitivity reactions (HSR).
***ABV/3TC is highly recommended [AI] only in patients with HIV-RNA ≤100,000 copies/mL; in those with HIV-RNA >100,000 copies/mL it should be only moderately recommended [BI].
****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; a new formulation of QD extended-release (XR) 400 mg tablet, which was demonstrated to be non-inferior to 200 mg BID standard formulation when used in combination with TDF/FTC, has recently approved by EMA.
	DRV/r (800/100 mg QD) [BI]	Limited use in naïve patients. Non-inferiority demonstrated only with respect to LPV/r (virological superiority at 192 weeks); 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 at 152 weeks; 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.
Acceptable	SQV/r (1000/100 mg BID) [CI]	Non-inferior to LPV/r (less hypertriglycerideamia), but with only a 48-week follow-up; higher cardiac toxicity; 200 mg RTV; superior number of pills; BID.
	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
2	ABC/3TC*	AZT/3TC	TDF+3TC		ABC/3TC** TDF+3TC AZT/3TC
3	AZT/3TC		AZT/3TC		
THIRD DRUG					
1	EFV ATV/r DRV/r RA	ATV/r, LPV/r, DRV/r, FPV/r	EFV, NVP-XR***	EFV LPV/r ATV/r NVP	DRV/r ATV/r LPV/r FPV/r
2	LPV/r FPV/r NVP	EFV, NVP, RAL	ATV/r, DRV/r	FPV/r DRV/r	EFV NVP RAL
3			NVP*, RAL, LPV/r	RAL	
4			FPV/r		

*If HIV-RNA before starting therapy <100,000 copies/mL, rank 1. *Lower risk of selecting resistance associated mutations for FTC compared to 3TC, especially if HIV-RNA is >100,000 copies/mL. *Nevirapine extended release (XR) with single tablet QD administration

HOW TO CONTINUE AFTER VIROLOGICAL SUPPRESSION: STRATEGIES FOR OPTIMIZING CART (Tables 10, 11)

The long-term treatment prospects and the availability of more compounds, more manageable and affected by different toxicities, enhance a tailored approach to cART management in order to maintain viroimmunological efficacy. Optimizing cART in a patient with persistent suppressed HIV viremia indicates the best strategies of therapeutic switching, with different purposes and rationale, but with mutual principles. The main recognized strategies are:

1. A reduction in the number of ARV drugs (schematic simplification);

2a. A reduction of daily doses and pill burden, but still in a triple cART regimen (management simplification);

2b. Other switching strategies with a triple drug combination, not included in the above conditions.

Therefore, the potential benefit and risk of tailored strategies should be accurately evaluated and discussed, and targeted to the needs of the single patient. The main reason leading to this choice may be:

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

TABLE 10 - *The reduction of the number of ARV drugs (schematic simplification).*

Type of switch	*Aims*	*Other potential benefits*	*Potential disadvantages*	*Degree recomm. level of evidence*
From three drugs to LPV/r monotherapy (400/100 mg BID)	Reduce toxicity	Reduce NRTI toxicity and possible previous NNRTI toxicity	Increase in pill burden/number of doses except for current 2NRTI + LPV/r regimens; gastrointestinal and metabolic side-effects; increased CVD risk in the long-term; lower virological efficacy than triple therapy; possible limited efficacy in reservoirs; contraindicated in HBsAg+	[BI]
From three drugs to DRV/r monotherapy (800/100 mg QD)	Reduce toxicity; simplifying from BID	Reduce NRTI toxicity and possible previous NNRTI toxicity; simplifying from BID	Virological efficacy not certainly non-inferior than triple therapy; possible limited efficacy in reservoirs; contraindicated in HBsAg+	[BI]

TABLE 11a - *The reduction of daily doses and pill burden (management simplification)*

Type of switch	*Aims*	*Other potential benefits*	*Potential disadvantages*	*Degree recomm. level of evidence*
From single compounds to fixed-dose combinations	Improve adherence and quality of life	Coformulation	None	[AII]
From NVP BID a NVP-XR QD	Improve adherence and quality of life	Lower pill burden and number of doses	None	[AI]
From PI/r to EFV	Reduce toxicity	Lower GI side-effects, coformulation	Neuropsychiatric side-effects; lower genetic barrier	[AI]

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Type of switch	*Aims*	*Other potential benefits*	*Potential disadvantages*	*Degree recomm. level of evidence*
From PI/r to NVP	Reduce toxicity	Lower GI and metabolic side-effects	Cutaneous rash and liver enzyme elkevations in the short term; lower genetic barrier	[AI]
From PI/r to raltegravir	Reduce toxicity	Lower GI and metabolic side-effects	Lowere genetic barrier; no-inferiority not achieved in a study; BID regime; not recommended in previously documented NRTI failure; use only after at least 6 months of virological suppression	[BI]
From enfuvirtide to raltegravir Reduce toxicity	Reduce toxicity	Reduce cutaneous adverse reactions in site of injection; more manageable; improve QoL	None	[AI]

TABLE 11b - *Other switching strategies.*

Type of switch	*Aims*	*Other potential benefits*	*Potential disadvantages*	*Degree recomm. level of evidence*
From tymidine NRTI or ddI to TDF or ABC	Reduce lipoatrophy and other toxicities; Lower pill burden and number of doses	Reduce toxicity; increase convenience; improve adherence		[AI]
From TDF to ABC	Reduce specific toxicity	Lower renal and bone toxicity	Increase dyslipidemia	[AIII]
From ABC to TDF	Reduce specific toxicity	Lower dyslipidemia	Reduce renal and bone toxicity	[AIII]
From EFV to NVP	Reduce specific toxicity	Lower dyslipidemia; better CNS penetration/effectiveness	Cutaneous rash and liver enzyme elevation in the short term; no coformulation	[AIII]
From NVP to EFV	Reduce specific toxicity	Coformulation	Increae dyslipidemia; neuropsychiatric side-effects	[AIII]
From LPV/r to ATV/r or DRV/r QD	Reduce specific toxicity	Lower dyslipidemia and GI side-effects; Lower pill burden and number of doses	No RTV coformulation; hyperbilirubinemia with ATV/r	[AI]
From DRV/r BID to DRV/r QD	Simplification	Simplification (lower pill burden and number of doses); lower dyslipidemia	In case of lack of DRV resistance-associated mutations only	[AI]
From ATV/r to ATV	Reduce specific toxicity	Improve hyperbilirubinemia, slight improve of dyslipidemia	Unboosted ATV not approved in Italy; lower genetic barrier; not indicated in association with TDF or PPI	[BI]*
*Indicated in patients with RTV intolerance; advisable TDM monitoring.				

MANAGEMENT OF THERAPEUTIC FAILURE (Tables 12-15)

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+ lymphocyte 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 12 - *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 13 - *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 14 - *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 15 - *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 with 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 to obtain and maintain both the viro-immunological and clinical success of treatment [AII]. High-level adherence to antiretroviral drugs has a pivotal role in reducing the risk of HIV transmission, especially in HIV serodiscordant couples [AII].
In the clinical setting, the patient's self-reported adherence, if investigated in a non-judgmental, 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].
The quality of the physician-patient relationship, the role of nursing staff, a multidisciplinary approach to care, together with the contribution of peer individuals, are all relevant for both adherence monitoring and supporting the optimal assumption of antiretroviral drugs [BII].
Simplified antiretroviral dosing with fixed-dose combinations has been shown to promote adherence to the antiretroviral therapy [AI].
In the clinical setting, it is recommended to in-

vestigate the presence of psychiatric disorders and depression in order to consider a specific treatment. Self-reported symptoms should be investigated, and if associated with therapy, a treatment modification should be considered [BII].
The 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" and multidisciplinary approach combining strategies related to antiretroviral management with educational and behavioural intervention 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], and using tools for screening of depression (e.g. CES-D and CES-D10) could be useful.

PHARMACOLOGICAL MONITORING
(Tables 16-17)

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

TABLE 16 - *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-drug-interactions.org**) for an exhaustive discussion of information pertaining to management of pharmacological interactions.

TABLE 17 - *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 18)

TABLE 18 - *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 COMORBIDITIES (Tables 19-23)

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 the 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 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 19 - *Risk factors for non-infectious comorbidities associated with HIV infection*

	Heart	*Kidney*	*Bone*	*Liver*	*Cancers*	*Lipodystrophy*	*Sexual dysfunction*
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 20 - *Screening strategies for non-infectious comorbidities associated with HIV infection.*

	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with 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	
	Current lifestyle: - Use of psychotropic medications or drugs (alcohol, smoking, illicit drugs) - diet - physical activity	+	+	every 6-12 months	More frequent discussion with the patient of healthy lifestyle and habits is recommended. Toxic alcohol damage is expressed in consumption exceeding 30 grams/day in males and 20 grams in females)
Body composition	Measurement of body mass index and waist circumference	+	+	once a year	
	Clinical assessment of lipodystrophy	+	+	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].

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	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with cart*	*Comments*
	Anamnesis of sexual life: - Safe sex - Sexual dysfunction - Reproductive counseling	+	+	once a year	Sexual dysfunction can be investigated by self-reported questionnaire. Periodical gynecologic evaluation is advisable.
Cardio-vascular disease	Assessment of overall risk	+	+	once a year	Using algorithms such as *Framingham* (http://hp2010.nhlbihin.net/atpiii/CALCULATOR.asp?usertype=prof), or o DAD 5 Year Estimated Risk calculator (http://www.cphiv.dk/TOOLS/DADRiskEquations/tabid/437/Default.aspx) Framingham risk score is appropriate in men older than 50 yrs, and in women aged >40 yrs. ECG is indicated for risk evaluation in patients with hyperthension and for assessment of cardiac conduction in patients taking protease inhibitors.
	Individualized clinical evaluation	+	+	once a year	
Hypertension	Blood pressure	+	+	once a year	
Dyslipidaemia	TC, HDL Col, LDL Col, TG	+	+	once a year	
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	Frequency of checks must increase before and during treatment with hepatotoxic drugs
	Liver ultrasonography in patients with liver enzyme elevation	+	+	once a year	
Kidney disease	Risk assessment	+	+	once a year	
	eGFR estimated with MDRD or *Cockroft-Gault* CKD-EPI calculators	+	+	every 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	See above for the frequency of assessment. With proteinuria ≥1 +/- eGFR <60 ml/min measure protein/creatinine in urine is advisable. In patients starting a tenofovir-containing regimen the initial assessment including plasma phosphate level must be carried out after 4 weeks and every 3-12 months thereafter.

	Assessment	*At HIV diagnosis*	*Before start of cart*	*Follow-up freq. with cart*	*Comments*
Bone disease	Height measurement	+	+	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	Major risk factors: hypogonadism, family history of fractures, BMI <19 kg/m^2, hypovitaminosis D, smoking, sedentary lifestyle, history of low impact fractures, advanced age, female gender, menopause or amenorrhea, habitual alcohol excess (>3 units/ day), steroids exposure for >3 months.
	Estimate of risk of fractures in subjects aged >40 years with FRAX®	+	+	every year	Employing algorithms as FRAX® (http://www.shef.ac.uk/FRAX/tool.jsp)
	Vitamin D dosage	+	+	every year	To be performed annually, preferably in autumn or spring, if risk factors or diseases related to ospeoporosis are present (chronic kidney disease, rheumatoid artritis, chronic inflammatory bowel diseases, hyperparathyroidism) [AII].
	Examination of bone mineral metabolism (at least 1 re-absorption *marker* and 1 deposit *marker*) and PTH	+	+	every year	[AII]
	DXA scan of the lumbar spine and hip or densitometry surrogate tests		+	every 2 years	DXA is indicated when, in addition to HIV, at least 2 of the major risk factors for osteoporosis are present [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 21 - *Principal toxicities attributable to different ARV classes and single drugs.*

	Rash - hypersensitivity	*Gastro-intestinal*	*Hepatic toxicity*	*Cardio-vascular*	*Bone/ muscle*	*Renal toxicity*	*Nervous system*	*Lipody-strophy*	*Metabolic alterations*
NRTI			X				X	X	
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
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

Evaluation of the risk of non-infectious comorbidities is based on progressive steps which may need multispecialistic intervention:

- Step 1: assessment of traditional risk factors for each non-infectious comorbidity. HIV represents an independent risk factor for organ disease [AII].
- Step 2: stratification of clinical risk by diagnostic algorithms. When specific HIV-related risk estimators are lacking, risk estimators of general population could be used [AII].
- Step 3: the vulnerability of single patients should be evaluated.

TABLE 22 - *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. 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 Discuss the risk of smoking relapse after cessationalso in the long-term , considering the process of fighting smoking craving.
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 g/day for females and <30 g/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. Reduction of alcohol intake to less than 20-40 mg daily, especially in patients with liver diseases, low adherence to antiretroviral therapy, poor immunological response, cancers, previous tuberculosis, diarrhea.
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 23 - *Identification and management of patients at high risk of cardiovascular disease.*

<table>
<tr><td colspan="8">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="8">Advise on diet and lifestyle in all patients</td></tr>
<tr><td colspan="8">Consider individualized modification of ARV therapy in patients with high CV risk</td></tr>
<tr><td colspan="8">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="3">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="3">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="3">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>

TABLE 24 - *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.

TABLE 25 - *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. Considering that in some individuals (especially those with very low 25-OH vitamin D plasma levels) regular nutritional supplementation may not be able to obtain optimal level, retesting plasma levels after 6 months from nutritional supplementation is advisable. Correct assessment of the bone structure cannot be separated from a study mineral metabolism.	The bone toxicity of tenofovir exceeds that of other antiretrovirals, and 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. If possible, control of 25-OH vitamin D levels after 6 months from nutritional supplementation is advisable, in order to assess reaching of optimal plasma levels. 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.

TABLE 26 - *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. 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. Lipodystrophic mixed phenotype or due to central accumulation has been associated with an increase of overall mortality and to an increased risk of cardiovascular events.	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. 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. In *naïve* patients EFV has been associated with an increased risk of lipoatrophy compared with ATV/r. In naïve patients starting treatment with an ATV/r-containing regimen, an increased visceral fat accumulation than with EFV was observed. In clinical trail on CCR5-antagonists or integrase inhibitors an association with an increased risk of lipoatrophy has not been observed. Consider Nucleoside Reverse Transcriptase Inhibitors (NRTI)-sparing regimens. Using these regimes may be associated with an increase risk of dyslipidemia. There are no antiretroviral therapy switch strategies with proven efficacy in the treatment of lipo-hypertrophy. In patients taking PI/r, the association with fluticasone (or other inhalation corticosteroids) should be avoided due to an increased risk of Cushing syndrome or of aseptic osteonecrosis.

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Prevention	*Management*
	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].

TABLE 27 - *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 extra-renal factors; further, the correlation between creatinine and glomerular filtratation is not linear. Measurement urine over 24 hours, while more time-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 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 whenever GFR is below 60 ml/min and/or in the case of observation of proteinuria/ microhematuria. 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.

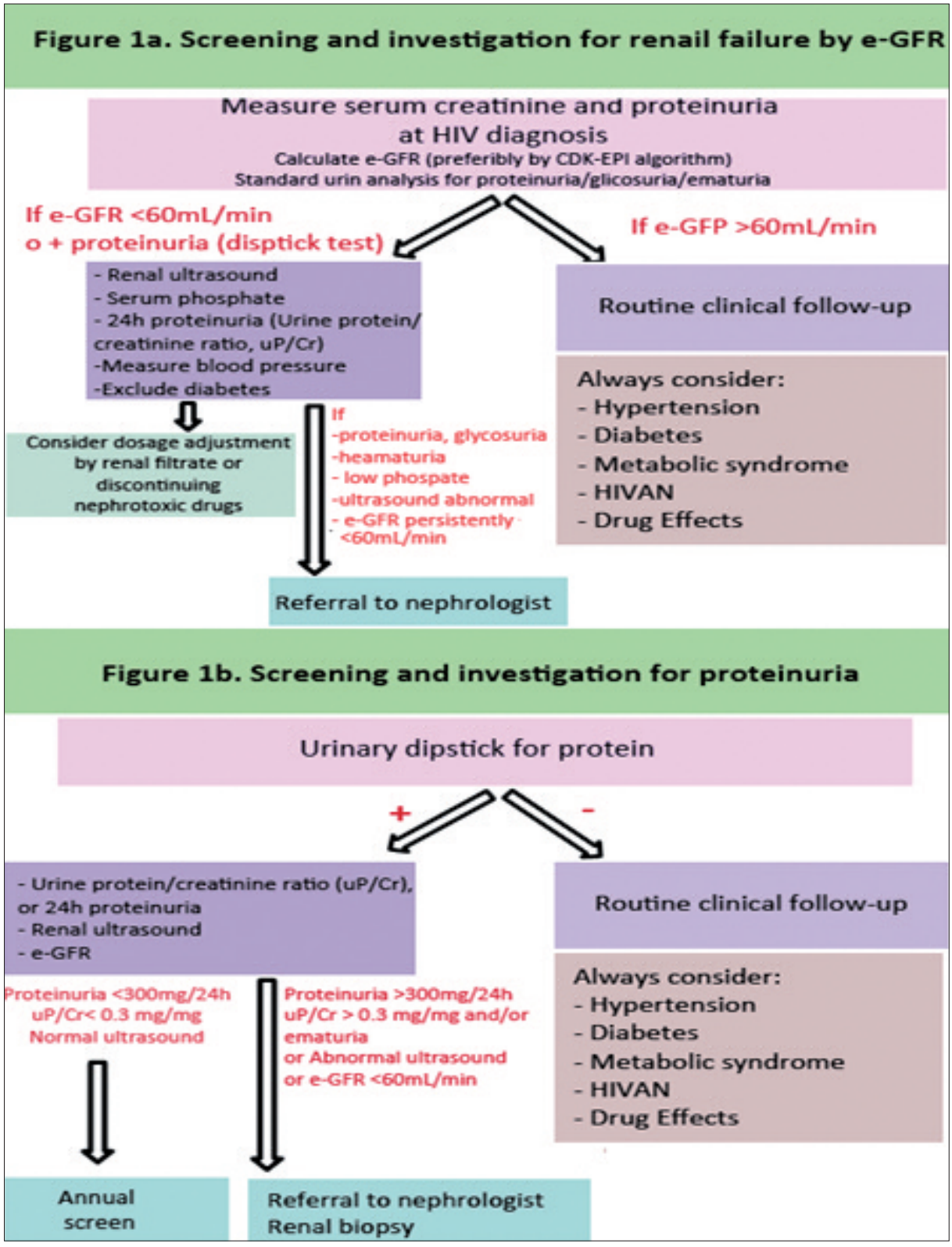

FIGURE 1 - *Clinical management of renal failure (1a) and proteinuria (1b).*

TABLE 28 - *Prevention and management of patients at high risk of vitamin D deficit*

Prevention	*Management*
Factors associated with low level of vit D are represented by coloured skin, low intake of vit D, lack of sun exposure, defective intestinal absorption, obesity, cronic renal impairement, exposure to some antiretrovirals. Role of antiretroviral therapy in general or as specific drugs is not completely defined. Vit D plasma levels represent an essential step in the diagnosis of osteomalacia/osteoporosis and in patients with cronic renal failure. When defect of Vit D is detected, plasma levels of parathyroid hormone (PTH), calcium, phosphorus, and alcaline phosphatase must be determined.	Replacement of vit D is recommended when plasma levels of 25(OH)D is less than 30 ng/ml (75 nmol/l). Hypophosforemia could be associated with TDF use. This loss of phosphorus, caused by damage of proximal tubulus could be independent from low levels of Vit D. Low levels of calcium and phosphorus combined with low levels of alcaline phosphatase could imply a defect of Vit D, whether or not associated with osteomalacia.. Some experts suggest replacement of Vit D in all HIV-infected patients, without need of determining plasma levels. When deficit of Vit D is detected, a load dose followed by a manteinace treamtn is advisable. Although different regimens have been suggested, the load dose could be performed with two consecutive doses of 300.000 UI per os and manteinance with a dose of 7000 UI per os every 7 days. When a low intake of calcium with diet, a replacement is advisable. Replacement of Vit D has been associated with a reduced incidence of diabetes mellitus.

TABLE 29 - *Treatment of sexual dysfunctions in men infected by HIV.*

Treatment of erectile dysfunction	*Treatment of premature ejaculation*
It is based on type 5 phosphodiesterase inhibitors (PDE5-Is), such as sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®) [113, 114]. The recommended initial dosages for patients with HIV treated with protease inhibitors are: I - Sildenafil 25 mg every 48 hours - Tadalafil 5 mg as initial dose (do not exceed dosages above 10 mg in the 72-hour period) - Vardenafil 2.5 mg as maximal dosage in 72-hour period Dosages of PDE5-Is higher than those generally recommended may be needed for patients receiving etravirine, a non nucleoside reverse transcriptase inhibitor [115]. The three drugs have to be taken in case of need half an hour before sexual intercourse); for tadalafil, in patients with treatment response in case of need and with presumably more frequent use of the drug (i.e. at least twice a week), a daily administration scheme with lower drug dosages may be suitable [113]. Treatment choice is based on personal preferences and on clinical experience.	Treatment of premature ejaculation is based on drugs as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, clomipramine, and topical anesthetics, though behavioural treatment and psychosexual counseling may be useful as well. It should be rememered that levels of clomipramine and of other tricyclic antidepressants) may increase with protease inhibitors and that these drugs should therefore be used at the lowest possible dosage [113, 114]. Dapoxetine, a potent SSRI with short action,is the only drug with approval in Europe for the treatment of premature ejaculation (to be taken in case of need) [113]. The frequency of recommended dosage is once every 24 hours. Evaluation of patient-reported benefits in respect to risks associated with drug intake needs to be carried out after the first 4 weeks of treatment (or after 6 doses) in order to define whether to continue or stop treatment.

HIV-ASSOCIATED NEUROCOGNITIVE AND PSYCHIATRIC DISORDERS

(Tables 30-33)

Neurocognitive disorders

The clinical outcome and quality of life of people with HIV infection can be profoundly influenced by the presence of neurocognitive 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 neurocognitive 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 30 - *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 Neurocognitive 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 neurocognitive 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;
- Cardiovascular risk factors, and/or disorders of the lipidic or glucidic metabolism;
- Co-infection with HCV.

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.

A possible cause of neurologic or cognitive impairment is the "CSF escape", defined as a condition of detectable HIV-RNA in CSF despite plasma virological suppression, or of higher HIV RNA levels in CSF than in plasma in patients on stable treatment. CSF escape has been associated with low CD4 nadir, long-term antiretroviral exposure, history of multiple failure, and poor adherence to treatment.

This condition, which seems to reflect a compartimentalized infection, is not necessarily symptomatic, and it has been observed in up to 10% of neuroasymptomatic patients.

On the other hand, cognitive impairment is only unfrequently associated with CSF escape, and it rather recognizes a multifactorial pathogenesis.

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.

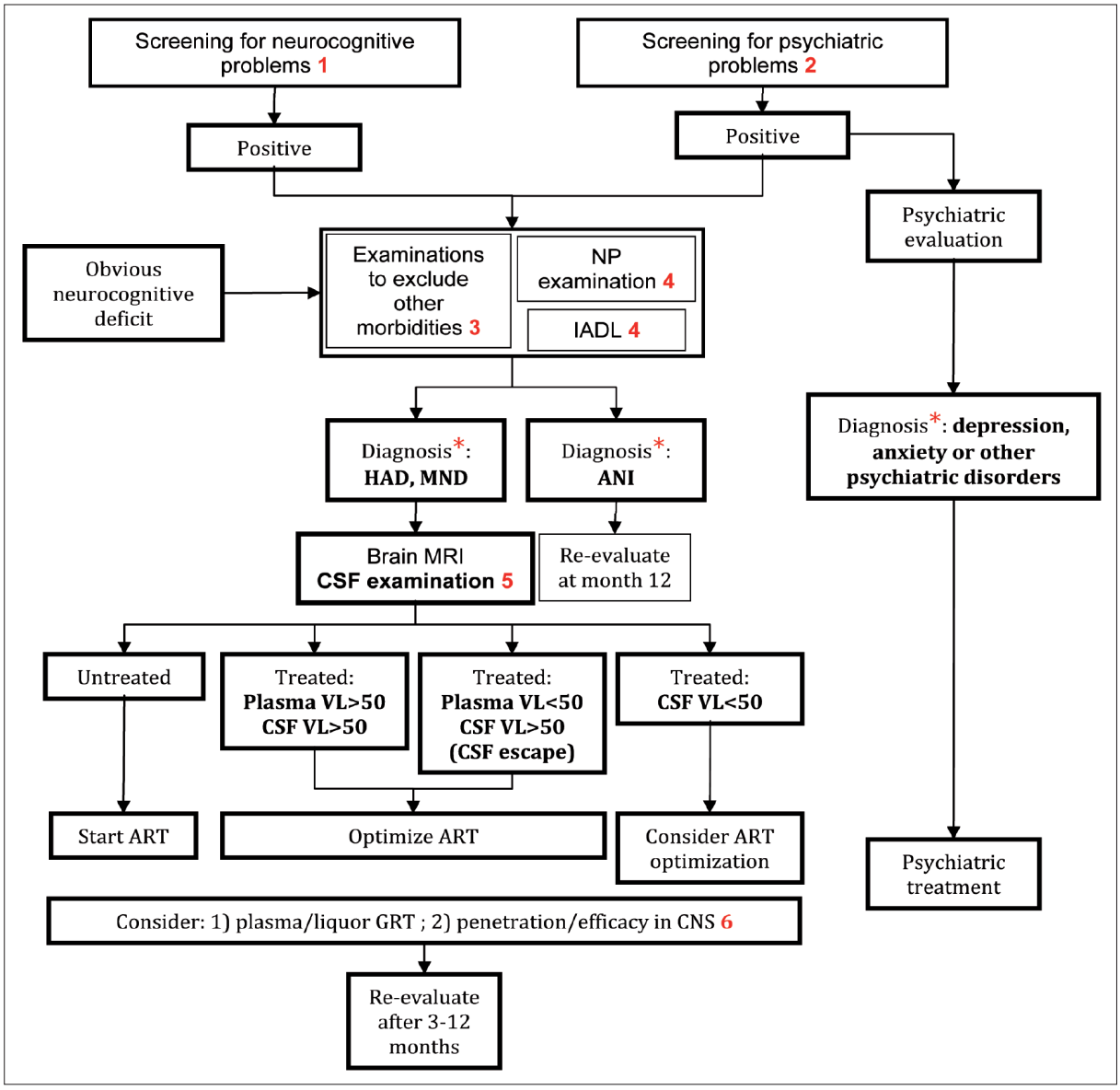

FIGURE 2 - *Diagnostic algorithm for the diagnosis and treatment of HIV-associated neurocognitive disorders (HAND). Abbreviation legend - IHDS: International HIV Dementia Scale; MMSE: Mini Mental State Examination; IADL: Instrumental Activities of Daily Living; NP Exam: Neuropsychological Examination; MRI: Magnetic Resonance Imaging of the brain with contrast media. Notes on the algorithm: 1. Neurocognitive screening: tools; a) Test of the three questions; b. IDHS; c. MMSE. 2. Psychiatric sceening: tools; a) Clinical history for previous psychiatric disorders or assumption of antipsycotic drugs; b. Patient Health Questionnaire Depression Scale (PHQ9); c. Generalized Anxiety Disorder-7 (GAD-7). 3. Examinations for conditions/comorbidities associated with non-HAND neurocognitive disorders: tools; a) Clinical history, clinical and neurological examination, blood tests, brain MRI, lumbar puncture. The objective is to exclude potential causes of neurocognitive impairment (current or previous abuse of drugs, antipsychotics or alcohol; cerebrovascula dementia; Alzheimer's disease; CNS infections or neoplasms; metabolic encephalopathy; cirrhosis). 4. Neuropsychological tests; Instrumental Activity of Daily Living (IADL). 5. Brain MRI; lumbar puncture and CSF examination. Examinations aims to identify HAND and exclude other pathologies. CSF analysis is primarily indicated to measure HIV-RNA level (concomitant with evaluation of plasma viremia) and detect drug resistance. Lumbar puncture is recommended in patients with MND or HAD [AII], and should be considered also in patients with ANI and risk factors for CSF viral escape (CD4 nadir <200 cell/mm3, long-term duration of therapy, history of multiple failures or multi-drug resistance, poor adherence). (In case of CSF escape, the same options for MND or HAND should be considered.). 6. Drugs recommended for high penetration and efficacy in the CNS. To define drugs with high 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], considering drugs with a CPE ranking score of 3 or 4. *In the case of negative results for cognitive impairment or psychiatric disorders, a new evaluation after 6-12 months is recommended.*

TABLE 31 - *Diagnostic route to diagnosis of HIV associated neurocognitive disorders (HAND)*

Level	*Examination(s)*	*Objective(s)*	*Population*
1	Screening test (3 questions, IHDL)	Identification of patients with possible neurocognitive disorders	All [AIII]
2a	Neuropsychological examination (NP)	Identification of patients with neurocognitive disorders. Together with IADL and exams to exclude other disorders: diagnosis of neurocognitive impairment and definition of severity.	Patients with suggestive clinical history or positive screening test [AII];
2b	IADL questionnaire	Evaluation of functional impact. Diagnosis of HAND severity	Patients with suggestive clinical history or positive screening test, or with altered NP exam [AII];
2c	Other exams (laboratory and instrumental tests, neurological examination, psychiatric evaluation*, brain MRI**, CSF examination**)	Exclude confounding disorders. Together with NP and IADL: diagnosis of HAND	Patients with suggestive clinical history or positive screening test, or with aletered NP exam and functional involvement [AII];
3	CSF analysis	Exclude confounding disorders. Assess HIV-RNA and GRT.	Patients with HAD or MND [AII]; to be considered in ANI with risk factors for "CSF escape" [BII].
GRT: *Genotypic Resistance Test*. *If altered psychiatric screening tests; **If MND or HAD			

TABLE 32 - *Antiretroviral therapy in patients with HAND*

	Clinical scenario and possible biological basis	*ARV therapy**
Off ARV therapy	Productive infection of CNS	In patients with MND or HAD, ARV therapy with 3 drugs, all with high penetration and efficacy in the CNS, also taking into account GRT in plasma and, if available, in CSF [AII]. In patients with ANI, no data currently suggest a treatment approach different from HIV general population. In patients with ANI and CSF VL>plasma VL, a regimen including drugs with elevated CSF penetration/efficacy could be advisable [BIII].
On ARV therapy, virological failure (plasma VL >50 copies/mL)	a) HIV RNA in CSF >50 copies/mL: possible productive infection of CNS; b) HIV-RNA in CSF <50 copies/mL: possible low-level HIV replication in CSF or CNS damage due to other factors.	In patients with MND or HAD, modification of ARV therapy on the basis of the GRT on plasma (a, b) and CSF (a), using ARV drugs more effective or at least equivalent to those included in current ART in terms of CNS penetration and efficacy. In patients with ANI, general criteria for management of virological failure.
On ARV therapy, suppressed viremia (plasma VL <50 copies/mL)	a) HIV-RNA in CSF >50 copies/mL: productive infection of CNS due to compartmentalised viral replication ("CSF viral escape"). Possible resistance in CSF and/or poor penetration/efficacy of ARV drugs in CNS; b) HIV-RNA in CSF <50 copies/mL: possible low-level HIV replication in CSF or CNS damage due to other factors.	In patients with MND or HAD, modification of ARV therapy on the basis of CSF GRT and previous resistance tests on plasma, preferring agents with high CNS penetration and efficacy (a) [AII]. Patients with ANI and CSF viral escape could benefit of treatment including drugs with high CNS penetration and efficacy [BIII].
*For drugs with elevated CNS penetration and efficacy, refer to CPE ranking score (see full version of the Guidelines), in which the drugs with higher penetration and efficacy are assigned a higher score (3 or 4).		

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

In the absence of MND or HAD it is important to identify the patients more at risk of developing symptomatic neurocognitive impairment and to employ effective strategies for its' prevention. In patients with ANI, monitoring of cognitive status is indicated every 12 months, in order to detect possible evolution toward symptomatic impairment [AII].

In patients without neurocognitive alterations, but with risk factors (CD4+ nadir <200 cells/μL, age >50 years, metabolic disorders, co-infection with HCV), neurocognitive monitoring by screening test is indicated every 12 months to evaluate possible evolution towards MND [AII]. In subjects without neurocognitive impairment and no risk factors, a re-evaluation every 2-3 years is advisable [AII]. In patients with ANI and risk factors of CSF escape (CD4 nadir <200 cell/mm3, long-term duration of therapy, history of multiple failures or multi-drug resistance, poor adherence), lumbar puncture with CSF examination should be considered [BII]. Cases with CSF escape could benefit of a treatment based on agents with high CNS penetration and efficacy [BIII].

TABLE 33 - *Monitoring the efficacy of antiretroviral therapy in HIV-Associated neurocognitive disorders (HAND).*

Level	*Scenario*	*Objective*	*Examinations*
1	Starting or changing cART, HAND	Initial evaluation of the efficacy of the (new) therapy on the neurocognitive impairment	After 6 months: NP exam [AII]
2°	cART monitoring: HAND with recovery of neurocognitive impairment	Monitor the efficacy of cART on the neurocognitive impairment	Every 12 months: NP exam [AII]
2b	cART monitoring: HAND with no recovery or worsening of neurocognitive impairment	Search for virological escape in the CNS Exclusion of other causes of neurocognitive 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]			

Psychiatric disorders

Psychiatric disorders may both cause cognitive problems and confound HAND diagnosis. They occur at a higher frequency in HIV-positive persons than in the general population, and include depression, anxiety, and other disturbances. Depression and anxiety may be associated with impaired memory and attention and mood changes, and these pictures may either represent a risk factor for, contribute to, or confound a diagnosis of HAND.

Indeed, there is a relationship between depression and cortical degeneration or neuropsichological abnormalities [13-17]. In this context, it is essential to recognize these disorders, to refer the patient to the specialist for additional diagnostic work-up and, in case, to initiate a specific treatment. To this aim, we suggest two simple and quick tests (5-7 min) that can also be administered by non-specialist personnel as a screening approach to identify psychiatric problems: the Patient Health Questionnaire Depression Scale (PHQ9) and the Generalized Anxiety Disorder-7 (GAD-7) (attached).

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 COMORBIDITIES

(Tables 34, 35)

Infection by hepatitis viruses

When to start antiretroviral therapy

Patients with hepatitis virus co-infection - Maintenance of CD4+ count over 500 cells/□L 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/□L 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 34 - *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
	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 abacavir in patients treated for HCV with low-dose ribavirin or that have to reduce ribavirin dosage due to side-effects (anemia); 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		

→

	Coinfection with HCV	*Coinfection with HBV*	*Cirrhosis*
	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.
In patients receiving telaprevir, do not use lopinavir/r, darunavir/r or fosamprenavir/r. Possible using atazanavir/r or efavirenz (increasing daily dosage of telaprevir up to 1125 mg TID). Use of telaprevir increases exposure to tenofovir. In patients treated by boceprevir, boosted protease inhibitors should be avoided. In general, use cautiously anti-HCV direct-acting antivirals (DAA) in antiretroviral setting, due to limited information and high-level drug-drug interactions with antiretroviral drugs.

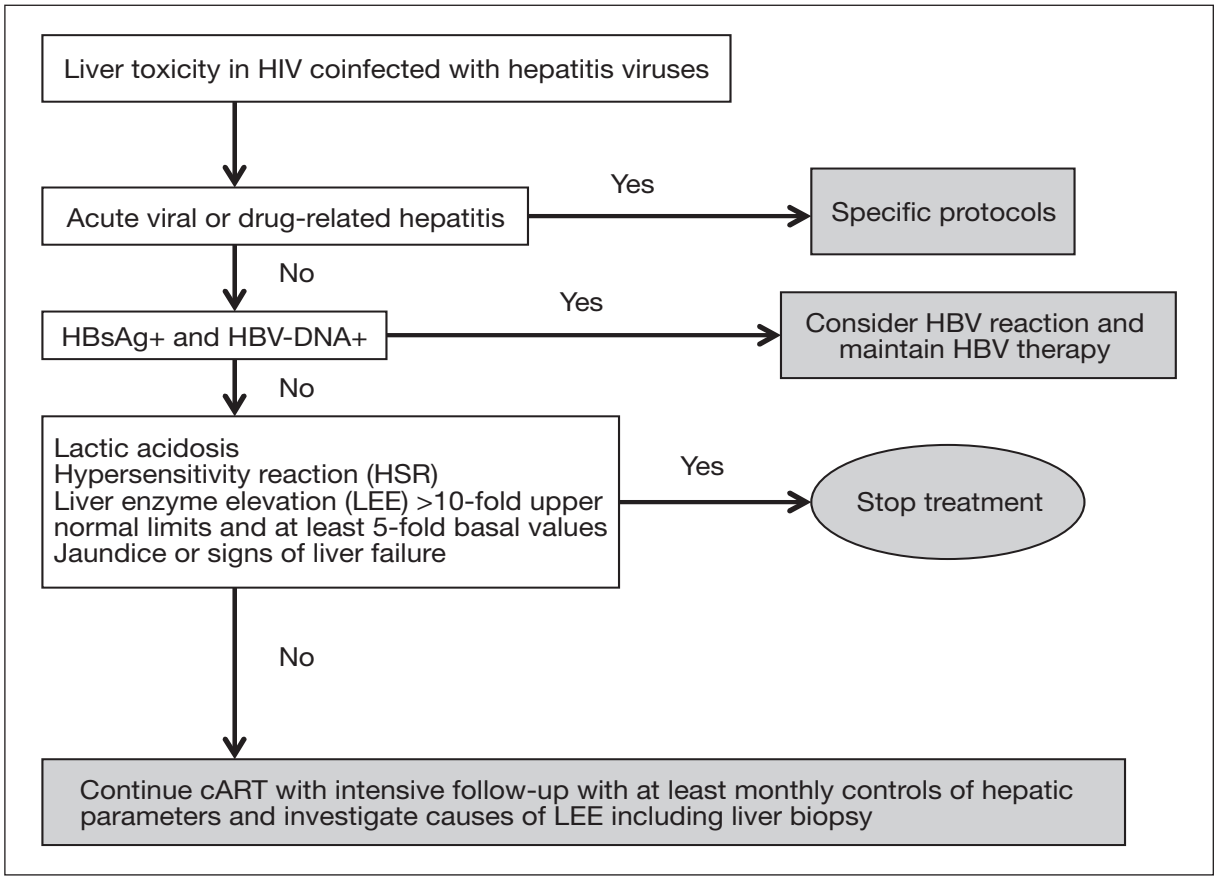

FIGURE 3 - *Management of liver toxicity in HIV-infected individuals treated with antiretrovirals.*

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 35 - *Principles of ARV management in HIV-infected patients with tuberculosis*

	Recommendations	*Comments*
When to start	Strongly recommended to start cART during anti-tubercular therapy, independently from CD4 count or plasma HIV-RNA levels [AI].	In patients with CD4 <50 cells/mm^3 initiation of ART is recommended at 2 weeks from starting of anti-tubercular therapy [AI]; In patients with CD4 50-500 cells/mm^3 initiation of ART is recommended from 2 weeks to 2 months from starting of anti-tubercular therapy [AI]; In patients with CD5 >500 cells/mm^3: initiation to be established on individual basis, according with cost-benefit evaluation
When to start	Strongly recommended to start cART during anti-tubercular therapy, independently from CD4 count or plasma HIV-RNA levels [AI].	In patients with CD4 <50 cells/mm^3 initiation of ART is recommended at 2 weeks from starting of anti-tubercular therapy [AI]; In patients with CD4 50-500 cells/mm^3 initiation of ART is recommended from 2 weeks to 2 months from starting of anti-tubercular therapy [AI]; In patients with CD5 >500 cells/mm3: initiation to be established on individual basis, according with cost-benefit evaluation
What to start with	EFV+2NRTI is the choice regimen to be combined with a rifampin-based tuberculosis regimen [BI]. Use of PI/r or PI (except for unboosted saquinavir) is feasible if combined with rifabutine [BII]. All these combinations should be used in patients with NNRTIs resistance or tolerance.	The use of PI/r or PI combined with rifampin is contraindicated.
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
(Tables 36, 37)

TABLES 36 - *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 [AII].
In patients with PCP initiation of ART is highly recommended within 2 weeks of the diagnosis of PCP [AI].
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 37 - *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
(Table 38)

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 [AI]. This therapeutic schema should be applied to all pregnant women with HIV, independent of the CD4 and HIV-RNA values [AI]. 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 [AII].

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 [AI]. If the woman is not yet undergoing treatment and there is indication for immediate treatment, it must be initiated as soon as possible [AII].
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 [AII].

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 [AII].

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 [AI].

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 [AIII] and in all those undergoing treatment with a confirmed detectable RNA [AI].
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 [AII].

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 [AI].
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 [AIII]. In case of elective interruption, in order to prevent the selection of resistant 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 [AII].

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.

TABLE 38 - *Considerations on cost-benefit ratio and on safety of single drugs during pregnancy.*

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	
Zidovudine	First choice as NRTI during pregnancy. It has been the first drug with a proven efficacy in prevention of mother to child transmission (MTCT) of HIV. Its inclusion in a regimen starting during pregnancy is advisable for its ability to cross the placenta. ZDV represents the drug with the most numerous reports on safety during pregnancy. If ZDV is included in the regimen at conception, in absence of toxicity or resistance, the continuation of the drug is advisable.
Lamivudine	First choice as NRTI during pregnancy. As for ZDV, a large experience on its use during pregnancy is available, in terms of tollerability and safety. It's active on HBV. Possible reactivation of HBV disease after stopping lamivudine.
Emtricitabine	Alternative choice to lamivudine, but less information available.
Tenofovir	Data available on safety of tenofovir during pregnancy are growing, but still limited. Risks of foetal abnormalities does not seem superior compared to that of other antiretrovirals. Toxicity characteristics could suggest potential risk of abnormal bone development in the foetus and nefrotoxicity in the mother. Preliminary studies with limited power did not demonstrated such effects. When tenofovir is included in the regimen, the monitoring of renal function is recommended. Due to its activity on HBV, the cost/ benefit ratio of using it during pregnancy may be favourable in HBV coinfected women who need treatment for HIV or HBV, if associated with nucleosides with anti HBV activity (lamivudine or emtricitabine). Reactivation of HBV disease is possible if the drug is stopped.
Didanosine	It is not considered a first choice- NRTI, but its use is acceptable. Data from Antiretroviral Pregnancy Registry (APR, which represent the widest case series on antiretroviral and congenital defects), demonstrated a slight increase of congenital defects in newborns exposed to DDI during the first three months of pregnancy, without any particular pattern of defects. Based on the current proportion of congenital defects in DDI-exposed newborns observed in APR (4.6%), as well as on lack of evidence of a particular pattern, this slight increase has not been considered as actually causative of increased risk of congenital defects. The association with stavudine has to be avoided in presence of alternative chances.
Abacavir	Potential risk of hypersensitivity reaction in patients with genetic predisposition (HLA-B*5701). Three nucleosides-based regimens containing abacavir showed less efficacy compared with NNRTI- or PI/r-based regimens and should be avoided in the presence of more efficacious alternative chances.
Stavudine	The association with DDI should be avoided in presence of alternative chances. Stavudine should not be associated with zidovudine for pharmacologic antagonism.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz	Use of efavirenz has been associated with a risk of abnormalities during embriogenesis. When prescribing Efavirenz to a child-bearing women it is recommended to inform the women on its potential risks. Its use should be avoided in women planning a pregnancy or without adequate contraception [AIII]. Similarly, the start of efavirenz must be avoided during the first tremester of pregnancy [AIII]. Recent data from meta-analysis as well as from Antiretroviral Pregnancy Registry, do not find that exposure to efavirenz during the first trimester is not associated with a significantly higher risk of congenital defects than that observed with other antiretrovirals. In women who become pregnant during an efavirenz-based regimen, considerations on interrruption of pregnancy or change of therapy must take into account the period of pregnancy as well as the long half-life of the drug, considering that the closing of neural tube occurs during the sixth week of pregnancy.
Nevirapine	The risk-benefit ratio of starting a nevirapine-based regimen during pregnancy is still controversial. Women starting nevirapine at CD4+>250 cells/mmc, an increased risk of epatotoxicity has been described, apart from concomitant rash, even lifetreathning. This increased risk of liver toxicity has not been confirmed in all studies of pregnant women and data from multicenter cohort studies did not find an increased risk in women on nevirapine-based regimens compared to other aniretrovirals. Nevertheless, HIV-pregnant women have an increased risk of epatotoxicity compared with non-HIV pregnant women. Al these considerations must be taken into account in the cost-benefit evaluation of using nevirapine during pregnancy.

→

Etravirine	Data on its use during pregnancy are not yet available.
Protease inhibitors (PI)	
Lopinavir/r	First choice among PI for use during pregnancy. Lopinavir represents the PI for which more information is available on its use during pregnancy. Data assessed a favourable balance between potency and safety in pregnancy.
Atazanavir	Exposure to atazanavir during pregnancy is increasing. Data are sill limited and risk of abnormalities sems to be not higher to those of other antiretrovirals. Theoretical probability of worsening of physiological hyperbilirubinemia of newborn. Potential reduced plasma levels if used without ritonavir or if associated with tenofovir.
Saquinavir	Limited data during pregnancy. To be boosted with ritonavir.
Fosamprenavir	Sufficient information on its use in pregnancy is not available.
Tipranavir	Sufficient information on its use in pregnancy is not available.
Darunavir	Sufficient information on its use in pregnancy is not available.
Nelfinavir	Drug of the most frequent use up to 2007, with a favourable safety profile. Between 2007 and 2008 it has been temporarely withdraw from commerce in Europe, for the presence of etilmetansulfonate (EMS), a potentiallly teratogen, mutagen and carcinogen compound. For its use during pregnancy, it must be considered that in clinical trials apart from pregnancy it demonstrated lower rates of virological response compared to LPV/r.
Indinavir	To use in the absence of other therapeutic chances, if associated with ritonavir. Theoretical probability of worsening of physiological hyperbilirubinemia of newborn.
HIV inhibitors of other drug classes	
Raltegravir	Although sufficient data for recommending its use during pregnancy do not exist, the drug could be potentially useful in highly viremic setting in the last period of pregnancy, when reducing the plasma viremia before delivery is mandatory.
Maraviroc	Sufficient information on its use in pregnancy is not available.
Enfuvirtide	Limited information on its use during pregnancy is available. The drug seems to not be able to cross the placenta, and it has been used unfrequently in the last period of pregnancy to riduce plasma viremia, particularly in presence of a multiresistant virus.

POST-EXPOSURE PROPHYLAXIS
(Tables 39, 40)

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, a 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 could 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 of bio-molecular techniques is not indicated for the purpose of ascertainment of infection [AII].
- Performance of ad hoc tests to determine re-

sistance 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 [AIII].
- Individuals taking PEP should receive an enhanced risk reduction and adherence counseling, and an active follow-up [AII].

TABLE 39 - *Recommendations for offering PEP*

a) OCCUPATIONAL EXPOSURE	
Exposure Mode	*Source Patient*
Needle used in vein or artery Deep lesion with needle or solid cutting device visibly contaminated with blood.	HIV+* or HIV negative but with history or current pathology indicative of very recent at risk exposure (e.g. acute viral hepatitis, STI, endocarditis of right heart) or Refusing to consent to serology test 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 load 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.	
b) NON OCCUPATIONAL EXPOSURE	
Exposure Mode	*Source Patient*
Receptive anal, vaginal, oral sex 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, STI, 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 intravenous drug abuse	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. ^the risk is lower if circumcised. 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].

In case of post-coital contrapception, PEP regimens including efavirenz or protease inhibitors boosted with ritonavir should be avoided. [AII].

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; for pregnant women is not recommended the use of efavirenz (possible teratogenicity), stavudine and didanosine (lactic acidosis), indinavir (hyperbilirubinaemia as birth approaches) [AII].

TABLE 40 - *Antiretroviral regimens recommended and alternative for PEP.*

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

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