Key questions in antiretroviral therapy: Italian Consensus Workshop (2005)

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A panel of leading Italian specialists in infectious diseases, virologists and immunologists met in Rome in 2005 to review critical data and discuss recommendations for each of the key questions in antiretroviral therapy today: When to start treatment? How to start? When to switch? What to switch to? Whether to stop or not to stop treatment, and how? The method of a nominal group meeting was used and recommendations were graded for their strength and quality using a system based on the one adopted by the Infectious Diseases Society of America. Main conclusions are summarized and critically discussed in this consensus statement, as well as some of the most recent data supporting these recommendations are provided.

Keywords: HIV, HAART, guidelines

Introduction

Highly active antiretroviral therapy (HAART) has revolutionized the clinical scenario of HIV infection in developed countries because morbidity and mortality due to opportunistic infections can be prevented or cured by HAART. However, several problems have arisen due to drug toxicity, tolerability, emergence of HIV resistance and diseases due to co-morbidities such as hepatitis co-infections and end-stage liver diseases. As a consequence, management of antiretroviral therapy is continuously evolving as well as recommendations of antiretroviral therapy guidelines.

It is important to recognize that many aspects are still unresolved and recommendations of current antiretroviral therapy guidelines are often based on inconclusive literature data or expert opinion. Moreover, specific characteristics of the HIV epidemic (e.g. prevalence of hepatitis co-infections) and clinical experience may influence expert opinion and HIV disease management in different countries. For these reasons, a consensus workshop of Italian HIV-treating physicians and experts in this field has been held, in order to review the current knowledge of antiretroviral treatment for adolescent and adult people affected by chronic HIV infection. Results of the consensus workshop have been used to set the basis for official antiretroviral therapy recommendations of the Italian Ministry of Health.

This report summarizes the main conclusions and recommendations from the consensus workshop. At the end of the document, a comparison with major guidelines in this field is provided.

Methods

Four experts in the HIV field prepared a draft of the consensus statements, grading the quality of each evidence after a careful review of the current literature data. Each of the four experts
addressed one of the four key questions in antiretroviral therapy today: (i) When to start treatment? (ii) How to start? (iii) When to switch? (iv) What to switch to? Whether to stop or not to stop treatment, and how? Statements were graded for their strength and quality using a system based on the one adopted by the Infectious Diseases Society of America (IDSA) (Table 1).

A qualified panel of Italian expert infectious disease clinicians, immunologists, virologists and HIV-treating physicians was convened in Rome in June 2005 for a 2 day workshop. On the first day, after two introductory lectures, the four experts who prepared the statements presented them. After a plenary discussion, each group of statements was reviewed by a working group of 10–15 HIV-treating physicians and, if necessary, re-formulated. On the second day, the revised statements were presented in a plenary session by a tutor selected from each group, modified if necessary after a plenary discussion and voted by all participants using a tele-voting system. All the participants voted on their degree of agreement with the statement and the strength of the recommendation. Participants ranked their agreement on a scale of 1 (complete disagreement) to 9 (complete agreement). Statements were accepted only when all the ranks of agreement were between 7 and 9, otherwise they were re-formulated again and re-voted.

1.0 When to start HAART?

Even though a precise algorithm is lacking, any guidelines regarding the initiation of HAART must be based, first of all, on the clinical, virological and immunological data concerning the risk of disease progression. Recent retrospective studies suggested that earlier HAART initiation correlates with protection against clinical progression. A series of papers (reviewed by Holmberg et al.) suggested that earlier initiation of HAART is also associated with lower risk of adverse events due to drug toxicity, although this was not confirmed by others. Possible implication of results from treatment interruption studies is that the immune system is better preserved despite drug discontinuation when HAART is initiated at higher CD4+ T-cell counts. It has been demonstrated that maintaining CD4+ T-cell count at levels higher than 500 cells/mm³ is associated with mortality comparable to that found in the HIV-negative general population. Lastly, the possible interaction with hepatitis co-infections and their treatment should be taken into consideration: the recent Italian consensus conference for treatment of co-infected patients stated that early HAART initiation in HIV/HCV patients could improve immune function, thereby increasing the efficacy and tolerability of the postponed anti-HCV treatment.

In conclusion, there is a tendency indicating that starting HAART earlier than stated by recent guidelines is better; however, this is still an individualized choice based on the patient case. The percentage of CD4+ T-cells over total lymphocytes in addition to absolute count should also be considered. Recommendations for when to start antiretroviral treatment by viro-immunological and clinical status are summarized in Table 2 and illustrated in the statements below.

Statement 1.1

Initiation of antiretroviral therapy is recommended for all symptomatic patients (classes B or C according to the CDC '93 classification, modified), at any CD4+ T-lymphocyte count and in all asymptomatic patients with CD4+ T-lymphocyte counts ≤ 200/mm³ (or <15% CD4+ over total lymphocytes) [A-I].

Statement 1.2

Antiretroviral therapy initiation is advised in cases of asymptomatic patients with CD4+ counts within the 201–350/mm³ range [B-II].

Statement 1.3

Initiation of the therapy in this case (patients with CD4+ counts ranging from 201 to 350/mm³) can be delayed solely when HIV-RNA is <30 000 copies/mL, CD4+ count decay is slow and individual factors with the potential to interfere with an optimum adherence or therapy outcome exist. However, if treatment is delayed in these patients, a strict immunological and clinical monitoring should be performed [C-II].

Statement 1.4

HAART initiation can be considered for patients with CD4+ T-lymphocyte counts ranging from 351 to 500/mm³ and who are selected according to rapidity or risk of HIV disease progression (indicatively measured as HIV-RNA >100 000 copies/mL and/or CD4+ loss >100 cells/mm³/year) [B-II].

Statement 1.5

Other factors that can contribute towards the decision to initiate HAART in these cases (patients with CD4+ counts ranging from 351 to 500/mm³) are age >50 years and the presence of chronic HCV and/or HBV co-infections [C-II]. Drug addiction constitutes a factor related to the increased clinical progression in patients undergoing therapy. Drug addiction by itself does not constitute a contraindication to the antiretroviral treatment; patients with such a risk behaviour must be initiated on substitute treatment programmes and receive adequate psychological and social support [A-II].

2.0 How to start HAART?

The choice of antiretroviral therapy should first of all ensure a favourable balance between efficacy, risk of toxicities and lack of future options due to emerging HIV drug resistance mutations (‘sequenceability’). The choice of first-line therapy lies between two nucleoside or nucleotide HIV reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) combination, or the same backbone with protease inhibitors (PIs). A nucleoside analogue backbone still remains an essential component of HAART. Available studies on NRTI sparing regimens have suggested that some of these are associated with less potency and/or more significant toxicities and/or lipid abnormalities, although the risk of lipoatrophy may be
First regimen effectiveness should be assessed by taking into account virological potency, CD4+ count increase, treatment adherence, drug interactions, durability of treatment response, "sequenceability", tolerability, co-morbidities, and number of tablets and daily dosages.

Given the significant and increasing prevalence of HIV drug resistant strains detected in patients prior to initiation of antiretroviral therapy, it is recommended to use drug resistance testing for choosing drugs in the first-line antiretroviral regimen. Use of drug resistance testing has been proven to be cost-effective in such a circumstance.

Table 3 summarizes drugs that are suggested for initial treatment use based on the availability of clinical trial results. Specific recommendations for how to start treatment are given in the statements below.

**Statement 2.1**

Not all possible NRTI backbones were compared in association with the same drug used as 'third' component in the combination. The use of any specific NRTI backbone, for which no data from prospective, randomized studies in association with a given third drug are as yet available, should be avoided [A-III].

**Statement 2.2**

Due to inferior virological efficacy and higher risk of emergence of resistance-associated mutations in the HIV reverse transcriptase domain, regimens including three NRTIs should be limited at present solely to cases where it is impossible to prescribe alternative regimens or as a consequence of extreme simplification in case of adherence difficulties [A-I].

**Statement 2.3**

When the third drug opted for is a PI/r, due to current clinical practice, extended use, and remarkable potency, lopinavir/r is to be considered the first choice today [A-I].

Other PIs boosted with ritonavir to be considered as second choices are as follows:

(i) fosamprenavir/r [B-I];
(ii) saquinavir/r [B-I];
(iii) indinavir/r [C-I].

The use of atazanavir/r is not yet approved in Europe for naive patients. However, data already available using atazanavir/r in drug naive patients suggest that this drug is a good alternative to lopinavir/r.

**Statement 2.5**

Nelfinavir is the only PI approved for use without ritonavir as a booster in treatment of naive patients. This drug demonstrated a lower genetic barrier than lopinavir/r and is, therefore, used as first-line treatment only in special cases (in the case of reduced virological potency, CD4+ count increase, treatment adherence, drug interactions, durability of treatment response, 'sequenceability', tolerability, co-morbidities, and number of tablets and daily dosages).

Table 2. Recommendations for when to start antiretroviral treatment

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>CD4+ T-cell count</th>
<th>Recommendation</th>
<th>Strength and quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant symptoms or syndromes (B or C classes as by CDC '93 classification, modified)</td>
<td>any</td>
<td>treat</td>
<td>A-I</td>
</tr>
<tr>
<td>No relevant symptoms or syndromes</td>
<td>CD4+ ≤ 200/mm³</td>
<td>treat</td>
<td>A-I</td>
</tr>
<tr>
<td>No relevant symptoms or syndromes</td>
<td>201/mm³ ≤ CD4+ ≤ 350/mm³</td>
<td>treat. Initiation of the therapy in patients with HIV-RNA &lt;30000 copies/mL and slow CD4+ count decay, can be deferred, with strict follow-up</td>
<td>B-II</td>
</tr>
<tr>
<td>No relevant symptoms or syndromes</td>
<td>351/mm³ ≤ CD4+ ≤ 500/mm³</td>
<td>may treat in case of rapid HIV progression (indicatively measured as HIV-RNA &gt; 100000 copies/mL and/or CD4+ loss &gt;100 cells/mm³/year). Treatment may also be proposed in absence of rapid HIV progression, depending on age and presence of hepatitis co-infections, especially when foreseen adherence is good</td>
<td>B-II</td>
</tr>
<tr>
<td>No relevant symptoms or syndromes</td>
<td>CD4+ ≥501/mm³</td>
<td>observe</td>
<td>A-II</td>
</tr>
</tbody>
</table>
contraindications or intolerance to the use of the first or second choice drugs, such as in the case of an elevated cardiovascular disease risk, advanced liver impairment or drug-drug interactions) [B-I]. Atazanavir could be proposed in the same circumstances [B-I], but it is not currently registered for use in naive patients.

Statement 2.6

The following NNRTIs are both suggested as first-line treatment, although recommended to a different extent and each with specific contraindications:

(i) efavirenz [A-I];
(ii) nevirapine [B-I].

The use of efavirenz has been associated with a lower risk of virological failure as compared with nevirapine, especially in patients whose HIV plasma viral load was high at baseline. However, with the number of patients enrolled in the reference study,17 the difference did not reach statistically significant levels. Efavirenz can be more convenient with respect to nevirapine because it is dosed once daily. The use of efavirenz is contraindicated during pregnancy and in women seeking a pregnancy and is advised against in potentially pregnant or child-bearing aged women who do not take adequate measures to avoid pregnancy.

The use of nevirapine is strongly advised against in women with CD4+ counts ≤250/mm³; the drug must be used with caution in patients suffering from chronic hepatitis due to HCV and/or HBV co-infections. The issue of an increased risk of hepatotoxicity in patients taking nevirapine with respect to efavirenz is a further limitation of the former drug although when this drug is used in patients whose CD4+ T-cell count is below cut-off (250 and 400/mm³ in females and males, respectively) the risk is minimized, especially in those who are not co-infected with hepatitis viruses.

Statement 2.7

The following associations of two NRTIs are recommended as first-line combinations, in association with either a PI/r (or PI) or with an NNRTI:

(i) zidovudine + lamivudine [A-I];
(ii) tenofovir + lamivudine or emtricitabine [A-I];
(iii) abacavir + lamivudine [A-I];
(iv) stavudine + lamivudine [B-I];
(v) didanosine + lamivudine or emtricitabine [B-II].

Stavudine + lamivudine is currently not suggested as a first-line option when other options are available which are less toxic and more convenient, particularly because of the risk of lipoatrophy due to stavudine, although potency data and short-term toxicity profile may not be prejudicial.18,19 Moreover, the stavudine 30 mg twice daily dose rather than the 40 mg twice daily dose might ameliorate mitochondrial-associated complications without compromising antiviral activity.20

The first-line association of abacavir + lamivudine should be carefully monitored, when used together with an NNRTI, due to the risk of reactions as a result of both hyper-sensitivity to abacavir and rash due to NNRTI.

Preliminary data from clinical trials suggest that the zidovudine + lamivudine combination is associated with a slower recovery of CD4+ cells in comparison with the abacavir + lamivudine and tenofovir + emtricitabine combinations.21,22 The clinical value of such observations deserves to be confirmed by further studies.

Table 3. Recommendations for how to start antiretroviral treatment

<table>
<thead>
<tr>
<th>Strength and quality of evidence</th>
<th>NRTI backbone</th>
<th>PI third drug</th>
<th>NNRTI third drug</th>
</tr>
</thead>
</table>
| A-I                             | zidovudine + lamivudine  
  tenofovir + lamivudine  
  or emtricitabine  
  abacavir + lamivudine | lopinavir + ritonavir | efavirenz |
| B-I                             | stavudine + lamivudine | fosamprenavir + ritonavir  
  saquinavir + ritonavir  
  nelfinavir  
  atazanavir ± ritonavir | nevirapine |
| B-II                            | didanosine + lamivudine  
  or emtricitabine | | |
| C-I                             | | indinavir + ritonavir | |

Notes:

(i) The following drugs are approved by the FDA and/or EMEA for once daily administration: lamivudine (300 mg, 1 pill); emtricitabine (200 mg, 1 pill); didanosine (250–400 mg, 1 pill); tenofovir co-formulated with emtricitabine (300/200 mg, 1 pill); abacavir co-formulated with lamivudine (600/300 mg, 1 pill); fosamprenavir + ritonavir (1400 + 200 mg, 4 pills), which is not currently registered in Italy for use in naive patients dosed once daily but only registered for twice daily use in these patients; atazanavir ± ritonavir (400 – 300 + 100 mg, 2–3 pills), which is not currently registered in Italy for use in naive patients; and efavirenz (600 mg, 1 pill).

(ii) The following drugs are not approved, but studies support once daily administration: saquinavir + ritonavir (variable doses, 7–12 pills); indinavir + ritonavir (variable doses, 5–7 pills); and nevirapine (400 mg, 2 pills), which is associated with higher hepatotoxicity risk when administrated once daily rather than twice daily.

(iii) The following drugs should not be administered once daily: stavudine (30–40 mg twice daily, 2 pills); zidovudine (250–300 mg twice daily); and not boosted protease inhibitors (variable doses).
Statement 2.8

There are contraindications to the use of some NRTI combinations:
(i) zidovudine + stavudine, due to the antagonism existing between the two drugs [A-I];
(ii) stavudine + didanosine, due to the synergic or additive mitochondrial toxicity [A-I];
(iii) tenofovir + didanosine in association with efavirenz [A-I] or with nevirapine [A-II], due to the high rate of early virological failure. Moreover, CD4+ T-cell decline despite virological suppression, pancreatitis, lactic acidosis and diabetes has been recorded with this combination.23

3.0 When and how to switch?

Reasons for changing antiretroviral therapy are as follows:
(i) failure of a first or subsequent antiretroviral treatment line because of (a) virological, (b) immunological or (c) clinical progression;
(ii) simplification because of (a) toxicity, (b) poor adherence or (c) patient choice (after consideration of the pros and cons and discussion with the treating physician).

The long-term, final objective of antiretroviral therapy consists of keeping HIV plasma viral load (HIV-RNA) levels as low as possible and for as long as possible. The attainment of undetectable HIV-RNA (<50 copies/mL) after HAART initiation facilitates the achievement of such a final objective. However, in case of repeated antiretroviral therapy failures, achieving undetectable HIV-RNA levels becomes increasingly difficult, especially if adequate programming according to a drug sequencing logic (‘sequenceability’) does not occur. In such cases, undetectability as an objective is progressively substituted by a relative reduction of HIV-RNA (‘as much as possible’), by the maintenance of a CD4+ count as high as possible and by the prevention of clinical events.24

The following approaches can be recommended to achieve these goals, as described in the statements below. Among the suggested approaches, the panel believes that it is important to appropriately address the causes of first-line treatment failure and switch therapy proactively, if necessary, in order to prevent deep salvage. Moreover, a new drug class (i.e. fusion inhibitors, namely enfuvirtide) and new generation PIs which are active against HIV strains resistant to other PIs (such as tipranavir and TMC-114) will soon be available in current clinical practice. When used in combination, they allow virological control to be regained and an increase in CD4+ T-cell count in a significant proportion of experienced patients.

Recommendations for how to switch in case of failure of first-line treatment are summarized in Table 4.

Statement 3.1

According to available data, the virological failure of a first-line therapy can be defined as follows:
(i) confirmed virological rebound (>50 copies/mL HIV-RNA) in patients with at least two previous undetectable HIV-RNA determinations [B-II];
(ii) presence of >50 copies/mL HIV-RNA in at least two subsequent determinations following 24 weeks of continuing antiretroviral therapy [B-III].

Since a correlation exists between the extent of early HIV-RNA reduction and the probability of subsequent achievement of undetectable HIV-RNA, the following definition of virological failure has also been suggested, even though measures to be taken in such a case are not precisely defined (apart from careful adherence assessment and correction):
(i) failure to reduce HIV-RNA by at least 1 log10 copies/mL (rebound after undetectability) within 4 weeks of continuing antiretroviral therapy [C-II].

Statement 3.2

Change in the therapeutic regimen is advised in case of confirmed HIV-RNA >50 copies/mL in at least two consecutive assessments following 24 weeks of a continuous first-line antiretroviral therapy following a proactive approach [A-II]. However waiting until HIV-RNA is >500–1000 copies/mL may still be recommended.

Statement 3.3

The immunological failure of any first-line therapy can be defined as follows: increase of <25–50 CD4+/mm3 compared with the baseline value following 24 weeks of therapy [B-II]. Immunological failure in the presence of suppressed HIV-RNA does not usually require a change in therapy [B-II]. In such a case, however, other causes of immune-suppression (toxicity...
of drugs, co-morbidities/co-infections) or the advisability of introducing an immune modulating therapy should be considered [C-II].

Statement 3.4
Suboptimal adherence is a possible reason for a therapy change, both in patients with documented therapeutic failure [A-II] or in those on an effective therapeutic regimen but needing therapy simplification [B-II]. In either condition, a periodical check of adherence appears to be an essential instrument of therapeutic monitoring [A-II].

Statement 3.5
In patients undergoing therapeutic failure, low adherence levels should be singled out from the possible causes, since approaches to the treatment can differ [B-III]. Suboptimal adherence remains a crucial factor that patients and clinicians should try to amend either when previous treatment is limited—with low but not suppressed plasma viral load and few drug resistance mutations at genotypic tests—or when treatment experience is more extensive and extensive cross-resistant patterns of HIV drug resistance have emerged. In fact, in both circumstances, increased adherence may contribute to maximum virological suppression, maintaining immune function and preventing clinical progression [A-II].

Statement 3.6
No intensification of the therapeutic regimen by the addition of a further drug is recommended at present, due to the risk of aggravating the dosage load and toxicity and of provoking a depletion of the pharmacological options more rapidly [B-I].

Statement 3.7
The change in therapy should be guided by the results of the resistance test [A-I]. The panel advises the genotypic resistance test even with a low number of copies (<1000 copies HIV-RNA/mL) and before any therapy modification has occurred [B-III].

Statement 3.8
In patients whose failures occurred on regimens subsequent to first-line therapy, the decision to switch treatment should be individualized according to the virological success that is possible to attain [based on the number of pharmacological options still active; genotypic sensitivity score (GSS)], the urgent need to prevent or keep the progression of the infection (based on the patient’s clinical history and present situation, CD4+ T-cell count and its decline), the need to keep pharmacological options open that can be used in potent regimens (according to current or future availability of new drugs), the risk of toxicity and the wishes of the patient [A-II].

Statement 3.9
It is important, first of all, to state that the expression ‘active drug’ refers to one that appears to be equipped with antiretroviral activity as a consequence of the indications provided by an examination of the therapeutic history and by the sum of the resistance tests performed during the treatment history [A-II].

Statement 3.10
In case of virological failure with initial regimens containing two NRTIs + PIs (or PI/r), a possible option consists of switching to regimens containing two NRTIs + NNRTI [B-II]. However, considering the low genetic barrier of NNRTI drug class, such an option can be risky in the case of an accumulation of mutations of resistance to the NRTIs, due to the possible rapid emergence of resistances of HIV to the NNRTIs. In such a case, it could be more advisable to switch to an alternative regimen containing PI/r [B-II]. This recommendation is also based on the following consideration: in case of virological failure with initial regimens containing PI/r, limited drug resistance has been shown to emerge, which may allow a wide number of subsequent treatment choices (‘sequenceability’) [B-II].

Statement 3.11
In case of virological failure with initial regimens containing NNRTIs, a possible option consists of switching to regimens containing PI/r because NNRTI class cross-resistance is almost complete until new generation compounds are available in routine clinical care (e.g. TMC-125) [B-II].

Statement 3.12
Antiretroviral therapy should be changed in patients having the availability of three active drugs, preferably belonging to two different classes [A-III].

When, according to resistance tests, the active pharmacological options are limited to only one active drug, switching can be delayed until the time a new combination with at least two active drugs can be constructed, and unless signs of immune- virological progression and/or a particularly reduced CD4+ count, accompanied by high plasma viral load levels exist and/or signs or symptoms indicative of HIV clinical progression are present [B-III].

Risk of progression can be reduced by continuation of the current therapy, even with ongoing viral replication without any further increase in the CD4 count [B-II].

Statement 3.13
The advent of a new antiretroviral class (fusion inhibitors, namely enfuvirtide) has brought substantial advantages in terms of probability of achieving undetectable plasma viral load even in patients heavily pre-treated with antiretroviral drugs; at the same time, increase of CD4+ T-cell counts in enfuvirtide-treated patients may be partly independent from the extent of plasma viral load reduction. The virological benefit is strictly dependent on the number of active drugs used in the backbone, however. When new potent ritonavir-boosted PIs are used in the combination (e.g. TMC-114), the rate of virological success may approximate that typically observed after treatment of naïve patients. This consideration may lead to an anticipated use of enfuvirtide alongside the treatment itinerary. However, unless these new drugs are available, the use of enfuvirtide is reasonably directed towards patients who have experienced the three antiretroviral drug classes (NRTI, NNRTI and PI), failing both PI and NNRTI in the previous treatment lines. Moreover, patients should have at least one additional active drug available [B-II/III]. Such a criterion
Table 5. Peculiarities of the present Italian statements with respect to other major guidelines

<table>
<thead>
<tr>
<th>Major questions</th>
<th>DHHS (2005)(^{32})</th>
<th>BHIVA (2005)(^{33})</th>
<th>IAS-USA (2004)(^{34})</th>
<th>French (2004)(^{35})</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to start?</td>
<td>Italian guidelines do not recommend treatment when CD4+ T-cell count is &gt;500/mm(^3), while DHHS guidelines suggest to do so with CD4+ T-cell count &gt;350/mm(^3), depending on plasma viral load (&gt;100,000 copies/mL)</td>
<td>Italian guidelines suggest to start treatment in patients whose CD4+ T-cell count is 351–500/mm(^3) for particular conditions (high plasma viral load and/or accelerated CD4+ decrease), while BHIVA guidelines do not recommend treatment in these patients</td>
<td>Italian guidelines recommend treatment when CD4+ T-cell count is 201–350/mm(^3) (deferring treatment in these patients should be viewed as an exception). IAS-USA guidelines suggest that, in these patients, initiation of therapy needs to be individualized</td>
<td>French guidelines do not recommend treatment when CD4+ T-cell count is ≥350/mm(^3), unless viral load is &gt;100,000 copies/mL</td>
</tr>
<tr>
<td>What to start with?</td>
<td>Italian guidelines consider both nevirapine and efavirenz as first options, although with different degree of recommendations, while nevirapine is a second-choice option by DHHS guidelines</td>
<td>NRTI regimens are discouraged. However, ZDV/3TC/ABC with TDF is a possible option when a PI or NNRTI based HAART cannot be administered</td>
<td>IAS-USA guidelines do not mention the recent observation of risk of early virological failure and toxicity associated with tenofovir/didanosine combinations</td>
<td>lopinavir, fosamprenavir, saquinavir and indinavir boosted with ritonavir are all preferred options zidovudine/lamivudine/abacavir is an option when plasma viral load is &lt;100,000 copies/mL no mention of risk of early virological failure and toxicity after tenofovir/ didanosine combinations</td>
</tr>
<tr>
<td>When to change?</td>
<td>Italian guidelines suggest that treatment switch may be performed after first virological failure when plasma viral load rebounds above 50 copies/mL or is still detectable after 24 weeks using ultrasensitive methods, while DHHS guidelines pose a limit of 400–5000 copies/mL before changing</td>
<td>BHIVA guidelines suggest treatment switch after first virological failure when plasma viral load is higher than 400 copies/mL (for plasma viral load &gt;1000 copies/mL, reliable resistance testing results are of benefit)</td>
<td>IAS-USA guidelines emphasize the importance of obtaining resistance testing results as soon as plasma viral load is 501–1000 copies/mL before changing</td>
<td>French guidelines recommend treatment switch when plasma viral load rebounds above 5000 copies/mL</td>
</tr>
<tr>
<td>How to change?</td>
<td>Italian guidelines recommend drug resistance testing even though viral load is &lt;1000 copies/mL treatment intensification strategies are considered by DHHS guidelines, not by Italian guidelines</td>
<td>BHIVA guidelines suggest a differential approach based on detected resistance mutations at first HIV drug resistance testing. No major differences with Italian recommendations are present</td>
<td>no specific recommendations are given in the IAS-USA guidelines with respect to treatment itinerary that may be followed after failure of different initial HAART regimens</td>
<td>treatment intensification strategies are considered when plasma viral load is &gt;5000 after 3 months of therapy evaluation of plasma drug concentrations is suggested</td>
</tr>
<tr>
<td>Whether and how to stop?</td>
<td>specific criteria for treatment interruption are suggested by Italian guidelines: (i) undetectable plasma viral load; (ii) permanently (&gt;1 year) high (&gt;500/mm(^3)) CD4+ and high nadir (&gt;250/mm(^3)). Therapy should be re-established while reaching a 350 CD4+/mm(^3) threshold, in any case</td>
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</table>
is currently in use for the prescription of enfuvirtide, as officially recommended by the Italian Ministry of Health.

Statement 3.14

It is important to prevent toxicity by selecting drugs in accordance with predictable risks which can ensue from the patient’s characteristics and to change them, if necessary, after an early diagnosis of toxicity events [A-III].

Some switching should be considered an alternative to, prior to or in addition to pharmacological interventions aimed at correcting toxicity (e.g. therapy for dyslipidaemia) [A-III].

In patients who have had persistently undetectable HIV-RNA for at least 6 months and immunological success, the simplification of the therapeutic regimen should be considered in order to improve their treatment adherence and quality of life and to reduce the risks of long-term toxicity [A-II].

4.0 Whether and how to stop?

The matter of therapy interruption or discontinuation is seen to be highly debated at the moment due to the variance in the data available today and their fragmentary nature. Moreover, a recent randomized controlled trial of CD4+ guided treatment interruption in patients with CD4+ T-cell count higher than 350/mm³ has been prematurely stopped due to a high rate of clinical failures in those randomized to stop treatment when CD4+ T-cell count was higher than 350/mm³ and re-treat when CD4+ T-cell count was lower than 250/mm³.

Further sophisticated markers might prove to be useful, aimed at individualizing treatment interruption strategies at least in patients whose risk of CD4+ T-cell depletion is smaller than in other individuals. Such developments are not included in current clinical practice and merit further investigation, however. Moreover, partial treatment interruption strategies in virologically failing patients with high CD4+ T-cell counts (either partial treatment interruptions with regimens including NRTIs or lamivudine monotherapy in patients with lamivudine-resistant virus) should be further investigated.

Statement 4.1

Full treatment interruption in patients with low CD4+ (e.g. ≤250/mm³, or ≤17%) is at present contraindicated as a result of the detection of a significant risk of AIDS-related morbidity and mortality in this setting [A-I/II].

Statement 4.2

Structured treatment interruption strategies with pre-defined time periods in patients with undetectable HIV-RNA are not recommended outside of controlled clinical trials, since these have been associated with a significant risk of emergence of HIV drug resistance, especially to drugs with a lower genetic barrier [B-I].

Statement 4.3

In order to reduce long-term toxicity and costs, CD4+-guided treatment interruption strategies can be taken into consideration in patients with undetectable HIV-RNA, with permanently (>1 year) high (>500/mm³) CD4+ and high nadir (>250/mm³), with recommendations for the re-institution of the therapy on reaching a 350 CD4+/mm³ threshold, in any case [B-II].

Statement 4.4

Treatment interruption strategies have also been proposed to revert HIV resistance mutations, restore antiviral efficacy, reduce toxicity and, possibly, hamper the accumulation of resistance mutation because selection pressure is absent during the interruption periods. However, these strategies have not been comparatively evaluated in different situations after HAART failure. For this reason, in patients with elevated CD4+ levels and detectable HIV-RNA, treatment interruption strategies should be limited to controlled clinical trials [B-I].

Statement 4.5

In case of the necessity/ advisability of interrupting NNRTI-containing regimens, the risk of a rapid emergence of HIV resistance to this class of drugs should be considered because of the long plasma half-life of these agents [A-II]. Whenever possible, it is advisable to stop these drugs while the others are maintained in the regimen for 10–14 days, and then proceed to the interruption of the remaining drugs [B-III]. During the 10–14 day discontinuation of the NNRTIs, some clinicians prefer to substitute such class of drugs with a PI (with or without a ritonavir “boosting”), in order to protect the backbone of the associated drugs from possible emergence of HIV drug-resistant strains [C-III].

5.0 Comparison with major guidelines

Major differences of the present guidelines with respect to others are summarized in Table 5.

With regard to the suggested time for starting treatment, DHHS (The US Department of Health and Human Services) guidelines are the most proactive because antiretroviral therapy is also proposed for patients whose CD4+ count is high when plasma viral load is >100,000 copies/mL. In contrast, BHIVA (British HIV Association) guidelines are the most restrictive in this respect.

With regard to the choice of initial antiretroviral drugs, there is a clear suggestion towards using efavirenz as the first-line option rather than nevirapine in the DHHS guidelines, but also Italian and BHIVA guidelines score these drugs differently. Stavudine is contraindicated by BHIVA guidelines. Initial regimens containing NRTIs are contraindicated by all the guidelines unless in special circumstances (i.e. extreme simplification in cases of adherence difficulties), but tenofovir + zidovudine + lamivudine + abacavir could be a second choice option for the BHIVA guidelines, as well as zidovudine + lamivudine + abacavir in the presence of plasma viral load <100,000 copies/mL for the French guidelines.

With regard to the time of switching first-line drugs because of virological failure, the present statements are the most proactive because treatment switching may be performed as soon as a confirmed rebound in plasma viral load is detected (>50 copies/mL) or undetectable viral load is not achieved after 6 months of continuous therapy.

With regard to the choice of second-line regimens, both the present statements and BHIVA guidelines advise against
intensification strategies. Moreover, both guidelines emphasize the fragility of the NNRTI genetic barrier in NNRTI-naive patients when resistance mutations to the NRTI backbone have been accumulated after failure of previous regimens.

Finally, the present guidelines recognize that treatment interruption is a reality in current clinical practice and suggest specific criteria to stop and resume treatment in special circumstances.

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Transparency declarations

We do not have any conflicts of interest to disclose that may bias the results of the Consensus Workshop. Statements as presented were generated from the consensus of all the participants who voted in a plenary session after critical discussion.

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