



# Enfermedades Infecciosas y Microbiología Clínica

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## Consensus statement

### Executive summary of the GESIDA/National AIDS Plan Consensus Document on antiretroviral therapy in adults infected by the human immunodeficiency virus (updated January 2015)



Expert Panel of GESIDA and the National AIDS Plan<sup>◇</sup>

#### ARTICLE INFO

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#### ABSTRACT

In this update, antiretroviral therapy (ART) is recommended for all patients infected by type 1 human immunodeficiency virus (HIV-1). The strength and grade of the recommendation vary depending on the CD4+ T-lymphocyte count, the presence of opportunistic infections or comorbid conditions, age, and the efforts to prevent the transmission of HIV. The objective of ART is to achieve an undetectable plasma viral load (PVL). Initial ART should comprise three drugs, namely, two nucleoside reverse transcriptase inhibitors (NRTI) and one drug from another family. Three of the recommended regimens, all of which have an integrase strand transfer inhibitor (INSTI) as the third drug, are considered a preferred regimen; a further seven regimens, which are based on an INSTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor boosted with ritonavir (PI/r), are considered alternatives. The reasons and criteria for switching ART are presented both for patients with an undetectable PVL and for patients who experience virological failure, in which case the rescue regimen should include three (or at least two) drugs that are fully active against HIV. The specific criteria for ART in special situations (acute infection, HIV-2 infection, pregnancy) and comorbid conditions (tuberculosis and other opportunistic infections, kidney disease, liver disease, and cancer) are updated.

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### Executive summary del Documento de consenso de GESIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2015)

#### RESUMEN

Se recomienda tratamiento antirretroviral (TAR) a todos los pacientes con infección por VIH-1, aunque la fuerza y gradación de la recomendación varían en función del número de linfocitos CD4+/ $\mu$ L, la existencia de enfermedades oportunistas o comorbilidades, la edad y la prevención de la transmisión del VIH. El objetivo del TAR es lograr una carga viral plasmática (CVP) indetectable. El TAR inicial debe ser una combinación de 3 fármacos, que incluya 2 inhibidores de la transcriptasa inversa análogos de nucleósidos (ITIAN) y otro de distinta familia. Tres de las pautas recomendadas, todas las cuales tienen un inhibidor de la integrasa (INI) como tercer fármaco, se consideran preferentes, y otras siete, basadas en un INI, un inhibidor de la transcriptasa inversa no análogo de nucleósidos (ITINN) o un inhibidor de la proteasa potenciado con ritonavir (IP/r), como alternativas. Se exponen las causas y criterios para cambiar el TAR en los pacientes con CVP indetectable así como en los que presentan fracaso virológico, en cuyo caso el TAR de rescate debe incluir 3 (o al menos 2) fármacos plenamente activos frente al VIH. Se actualizan los criterios específicos del TAR en situaciones especiales (infección aguda, infección por VIH-2, embarazo)

##### Palabras clave:

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o comorbilidades (tuberculosis u otras enfermedades oportunistas, enfermedad renal, hepatopatías y neoplasias)

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## Introduction

Since 1996, when the arrival of antiretroviral drugs made it possible to build potent combinations, antiretroviral therapy (ART) has led to huge health care benefits (reduced morbidity, mortality and transmission of the human immunodeficiency virus [HIV]). In parallel with these advances, ART has become complicated owing to the high number of drugs and families, as well as the many aspects affecting the appropriate choice of drugs (efficacy, toxicity, resistance, tropism, pharmacologic interactions, use in special situations, and cost-effectiveness).

The complexity and speed with which changes occur necessitate frequent updating of guidelines on ART. For the last 16 years, GESIDA and the National AIDS Plan have jointly edited a consensus document on ART in adults.<sup>1</sup> The present document updates previous recommendations in this population.

The objective of this consensus document is to provide health professionals who treat HIV-infected adults with up-to-date knowledge on ART and a series of recommendations based on scientific evidence that can act as guidelines in therapeutic decision making.

## Clinical and laboratory evaluation as a guide for ART

### Clinical evaluation

It is important to take an exhaustive clinical history, including physical and psychological data, treatment, habits, and risk practices. Specific aspects applying to women (e.g., desire to become pregnant and contraception) should be analyzed and a complete physical examination performed.

#### Recommendation

- HIV-infected patients should undergo a physical examination every year. Pharmacological treatment should also be evaluated and a clinical history taken (A-II).

### Laboratory tests

In addition to specific determinations associated with HIV infection and its consequences, other tests should be ordered to take account of previous infections or cardiovascular risk factors.

#### Recommendation

- The initial laboratory workup should include a complete blood count, general biochemistry, and serology testing (*Toxoplasma*, cytomegalovirus, syphilis, HAV, HBV, and HCV). Viral load, CD4+ T-lymphocyte count, and primary resistance to HIV and HLA-B\*5701 should also be determined (A-II).

### CD4+ lymphocytes

The number of CD4+ T lymphocytes is the main marker of the risk of progression and onset of non-AIDS events.

## Recommendations

- The absolute number and percentage of CD4+ T lymphocytes should be determined before initiating ART. Once therapy has started, these determinations should be made periodically to monitor the immune response (A-I).
- Determinations can be at longer intervals (up to 12 months) in stable patients with suppressed plasma viral load (PVL) and CD4+ T-lymphocyte counts >300–500 cells/ $\mu$ L (C-II).

### Plasma viral load

PVL is a marker of the risk of progression and transmission of HIV.

#### Recommendations

- PVL should be determined before initiating ART (A-II).
- PVL is the main parameter for evaluating the virological efficacy of ART and for defining virological failure (A-I).
- The objectives of virological suppression should be met both in ART-naïve patients and in those who have experienced previous therapeutic failure (A-II).
- PVL should be determined using a technique with a quantification limit of at least 50 copies/mL. The same technique should always be used (A-II).
- If decisions on therapy are to be taken based on PVL, they should be confirmed with a second determination (A-II).

### Plasma concentration of antiretroviral drugs

Plasma concentration of antiretroviral drugs is correlated with efficacy and toxicity; therefore, determination of their levels could prove useful in certain situations.

#### Recommendations

- Determination of the plasma concentration of antiretroviral drugs is not recommended for habitual monitoring of HIV-infected patients (A-II).
- Determination of the plasma concentration of antiretroviral drugs may be indicated in specific clinical situations (e.g., risk of pharmacological interactions, organ transplantation, extreme underweight or overweight, pregnancy, and renal or hepatic insufficiency) and to confirm suspected poor adherence to therapy (B-III).

### Resistance of HIV-1 to antiretroviral drugs

Viral genome mutations are the consequence of rapid HIV-1 turnover and error-prone reverse transcriptase. The emergence of resistant mutations is associated with virologic failure. Resistance mutations can be either primary or secondary to virologic failure.

#### Recommendations

- Genotyping of reverse transcriptase and protease to detect HIV resistance mutations should be performed in all patients at diagnosis of infection and before initiating ART if this is deferred (A-II).

- Integrase resistance testing should only be performed in cases with a high suspicion of transmission of resistance to integrase inhibitors (C-III).
- Genotyping should be performed for detection of HIV resistance mutations in all patients whose therapy has failed (A-I).

#### Determination of the HLA-B\*5701 allele

The presence of the HLA-B\*5701 allele is associated with hypersensitivity reaction to abacavir (ABC), a life-threatening multiorgan clinical syndrome observed during the first 6 weeks of treatment.

##### Recommendations

- HLA-B\*5701 should be determined in all patients before initiating an ART regimen containing ABC (A-I).
- ABC should not be prescribed if the result of the HLA-B\*5701 determination is positive (A-I).

#### Determination of tropism

A tropism assay is useful when prescribing maraviroc (MVC).  
Recommendation

- Viral tropism should be determined before starting therapy with a CCR5 inhibitor (A-I).

#### Initial antiretroviral therapy

The main objectives of ART are to reduce HIV-associated morbidity and mortality, restore and preserve immune function, prevent the harmful effect of viral replication on possible existing comorbid conditions, and prevent transmission of HIV.

#### When should ART be initiated?

##### Recommendations

- ART should be initiated in all HIV-infected patients to prevent disease progression, reduce viral transmission, and limit any harmful effects on possible co-existing comorbid conditions. The strength of the recommendation varies depending on the circumstances (see Table 1).
- Initiation of ART should always be evaluated on an individual basis. Both CD4+ T-lymphocyte count and PVL should be determined before initiating ART. Furthermore, the therapeutic regimen should be adapted to lifestyle, comorbid conditions, and possible drug interactions. The risk of poor adherence should also be assessed (A-III).

#### Which combination of antiretroviral drugs should be used?

##### Recommendation

- Initial ART can be a combination of 2 nucleoside reverse transcriptase inhibitors (NRTI) and 1 integrase strand transfer inhibitor (INSTI), 2 NRTI and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), or 2 NRTI and 1 ritonavir-boosted protease inhibitor (PI/r) (A-I). Preferred antiretroviral drugs are set out in Table 2.

#### 1. NRTI

The NRTI combinations of choice are considered to be those comprising tenofovir/emtricitabine (TDF/FTC) and those

**Table 1**

Indications for ART in patients with chronic HIV infection<sup>a</sup>

Condition/circumstance	Strength and grade
<b>General recommendation</b>	
ART should be administered to all HIV-infected patients. <sup>b</sup> The strength and grade of the recommendation varies depending on the circumstances, as follows:	
<i>Diseases classed as B or C by the CDC</i>	
	A-I
<i>CD4+ T-lymphocyte count</i>	
<350/ $\mu$ L	A-I
350–500/ $\mu$ L	A-II
>500/ $\mu$ L	B-III
<i>Comorbid conditions</i>	
HIV-associated nephropathy	
Chronic HCV infection	
Chronic HBV infection	
Age $\geq$ 55 years	A-II
High cardiovascular risk	
Neurocognitive disorders	
Cancer	
<i>Risk of transmission</i>	
Pregnant women	A-I
Heterosexual transmission	A-I
Transmission between MSM	A-III

**Abbreviations:** HIV, human immunodeficiency virus; CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; HBV, hepatitis B virus; MSM, men who have sex with men.

The patient's disposition and motivation are critical and should be taken into account when deciding when to start therapy.

<sup>a</sup> It is important to evaluate the antiretroviral drugs that comprise the initial regimen on an individual basis by weighing up the advantages and disadvantages of each of the options.

<sup>b</sup> Patients who maintain an undetectable viral load without ART (elite controllers) are considered an exception. In this case, the absence of data does not allow us to evaluate the beneficial effect of ART; therefore, no treatment recommendation can be established.

comprising abacavir/lamivudine (ABC/3TC), which should be administered as co-formulated preparations.

##### Recommendations

- The NRTI combinations of choice for initial regimens are TDF/FTC and ABC/3TC (A-I).
- Co-formulated preparations are recommended (A-II).
- TDF/FTC should be used with caution in patients with renal insufficiency (A-II).
- ABC/3TC should be used with caution in patients with a high PVL (>100,000 copies/mL) when combined with an NNRTI or a PI/r other than LPV/r (A-II).

#### 2. NNRTI

##### Recommendations

- The combination efavirenz (EFV)/TDF/FTC is considered an alternative option (A-I). The combination EFV+ABC/3TC should be avoided in patients with a PVL >100,000 copies/mL (B-I).
- EFV is contraindicated during the first trimester of pregnancy. Other options are recommended in women who do not use effective contraception. Similarly, EFV should be avoided in patients who perform dangerous tasks if they present symptoms of somnolence, dizziness, and/or difficulty concentrating (A-III).
- Nevirapine (NVP) is contraindicated in women with CD4+ T-lymphocyte counts >250 cells/ $\mu$ L and in men with >400 cells/ $\mu$ L (A-II).
- Rilpivirine (RPV) should not be administered to patients with a PVL >100,000 copies/mL (A-II).

**Table 2**  
Recommended combinations of ART<sup>a</sup>

Third drug	Regimen <sup>a</sup>	Remarks <sup>b</sup>	
<b>Preferred.</b> <i>Regimens whose efficacy in randomized clinical trials is superior to that of others (fewer virological failures and/or fewer discontinuations because of adverse effects) and that have a low risk of drug interactions. Can be applied to most patients.</i>			
INSTI	ABC/3TC+DTG	<ul style="list-style-type: none"> <li>- ABC is contraindicated in patients with a positive HLA-B5701 test result. When ABC is prescribed, all possible measures should be taken to minimize modifiable cardiovascular risk factors.</li> <li>- A coformulation (1 tablet) has been approved by the EMA, although it is not currently available in Spain.</li> <li>- Few data for patients with CD4+ &lt;200 cells/μL</li> </ul>	
	TDF/FTC+DTG	<ul style="list-style-type: none"> <li>- Use TDF with caution in patients at risk of renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> <li>- Few data for patients with CD4+ &lt;200 cells/μL</li> </ul>	
	TDF/FTC+RAL	<ul style="list-style-type: none"> <li>- Use TDF with caution in patients with risk factors for renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> </ul>	
<b>Alternatives.</b> <i>Efficacious regimens that are not considered preferential because their efficacy was lower than that of preferred regimens in clinical trials or because they have potential drawbacks or restrictions in their indication. However, they may be the regimen of choice for some patients.</i>			
NNRTI	TDF/FTC/RPV	<ul style="list-style-type: none"> <li>- Not indicated in patients with PVL &gt;100,000 copies/mL.</li> <li>- Can be regimen of choice in patients with PVL &lt;100,000 copies/mL (more efficacious than TDF/FTC/EFV), especially if simplicity is a priority</li> <li>- Few data for patients with CD4+ &lt;200 cells/μL.</li> <li>- Perform genotyping beforehand to rule out NNRTI resistance mutations.</li> <li>- Contraindicated in patients taking proton pump inhibitors.</li> <li>- Use TDF with caution in patients at risk of renal insufficiency; not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> <li>- Must always be taken with food.</li> </ul>	
	TDF/FTC/EFV	<ul style="list-style-type: none"> <li>- Avoid in women aiming to become pregnant and patients with neuropsychiatric disorders or suicidal ideation. Use with caution in patients who perform dangerous tasks.</li> <li>- Use TDF with caution in patients at risk of renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> <li>- Since few data are available on this regimen in patients with CD4+ &lt;200 cells/μL, it should be the regimen of choice in very immunodepressed patients, especially if simplicity is a priority (if the combination is available in a coformulation).</li> <li>- Perform genotyping beforehand to rule out NNRTI resistance mutations.</li> </ul>	
	TDF/FTC/EVG/COBI	<ul style="list-style-type: none"> <li>- Not indicated in patients with eGFR &lt;70 mL/min. Use with caution in patients with eGFR &lt;90 mL/min.</li> <li>- Can be considered the drug of choice when simplicity is a priority.</li> <li>- Few data for patients with CD4+ &lt;200 cells/μL.</li> <li>- Greater likelihood of interactions than with other regimens.</li> </ul>	
	TDF/FTC/EVG/COBI	<ul style="list-style-type: none"> <li>- Not indicated in patients with eGFR &lt;70 mL/min. Use with caution in patients with eGFR &lt;90 mL/min.</li> <li>- Can be considered the drug of choice when simplicity is a priority.</li> <li>- Few data for patients with CD4+ &lt;200 cells/μL.</li> <li>- Greater likelihood of interactions than with other regimens.</li> </ul>	
INSTI	ABC/3TC+RAL	<ul style="list-style-type: none"> <li>- ABC is contraindicated in patients with a positive HLA-B5701 test result. When ABC is prescribed, all possible measures should be taken to minimize modifiable cardiovascular risk factors.</li> </ul>	
	PI/r	TDF/FTC+DRV/r or DRV/COBI <sup>c</sup>	<ul style="list-style-type: none"> <li>- Use TDF with caution in patients at risk of renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> <li>- Since sufficient data on this regimen are available for patients with CD4+ &lt;200 cells/μL, it can be used in very immunodepressed patients, especially when it is necessary to administer a regimen with a high genetic barrier (patients with poor adherence).</li> <li>- Combination of PI/r and TDF increases the risk of nephrotoxicity.</li> <li>- Greater likelihood of interactions than with other regimens.</li> </ul>
		TDF/FTC+ATV/r or ATV/COBI <sup>c</sup>	<ul style="list-style-type: none"> <li>- Avoid in patients taking proton pump inhibitors.</li> <li>- Use TDF with caution in patients at risk of renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> <li>- Since sufficient data on this regimen are available for patients with CD4+ &lt;200 cells/μL, it can be used in very immunodepressed patients, especially when it is necessary to administer a regimen with a high genetic barrier (patients with poor adherence).</li> <li>- Combination of PI/r and TDF increases the risk of nephrotoxicity.</li> <li>- Greater likelihood of interactions than with other regimens.</li> </ul>
	ABC/3TC+ATV/r or ATV/COBI <sup>c</sup>	<ul style="list-style-type: none"> <li>- Avoid in patients with PVL &gt;100,000 copies/mL.</li> <li>- Avoid in patients taking proton pump inhibitors.</li> <li>- ABC is contraindicated in patients with a positive HLA-B5701 test result. When ABC is prescribed, all possible measures should be taken to minimize modifiable cardiovascular risk factors</li> <li>- Greater likelihood of interactions than with other regimens</li> </ul>	
<b>Other possible regimens.</b> <i>These regimens have also demonstrated efficacy; however, either available evidence is considered insufficient or the regimen has drawbacks with respect to regimens considered preferred or alternative.</i>			
NNRTI	ABC/3TC+EFV	<ul style="list-style-type: none"> <li>- Avoid in patients with PVL &gt;100,000 copies/mL.</li> <li>- Avoid in women aiming to become pregnant and patients with neuropsychiatric disorders or suicidal ideation. Use with caution in patients who perform dangerous tasks.</li> <li>- Perform genotyping beforehand to rule out NNRTI resistance mutations.</li> <li>- ABC is contraindicated in patients with a positive HLA-B5701 test result. When ABC is prescribed, all possible measures should be taken to minimize modifiable cardiovascular risk factors.</li> </ul>	
	TDF/FTC+NVP	<ul style="list-style-type: none"> <li>- Do not initiate in women with CD4+ &gt;250 cells/μL or in men with CD4+ &gt;400 cells/μL.</li> <li>- Perform genotyping beforehand to rule out NNRTI resistance mutations.</li> <li>- Use TDF with caution in patients at risk of renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> </ul>	
PI/r	ABC/3TC+DRV/r or DRV/COBI <sup>c</sup>	<ul style="list-style-type: none"> <li>- ABC is contraindicated in patients with a positive HLA-B5701 test result. When ABC is prescribed, all possible measures should be taken to minimize modifiable cardiovascular risk factors.</li> <li>- Evaluate possible interactions.</li> </ul>	
	TDF/FTC+LPV/r	<ul style="list-style-type: none"> <li>- Avoid in patients with hyperlipidemia and/or high cardiovascular risk.</li> <li>- Use TDF with caution in patients at risk of renal insufficiency. Not recommended in patients with eGFR &lt;50 mL/min unless no alternatives are available.</li> <li>- Combination of PI/r and TDF increases the risk of nephrotoxicity.</li> <li>- Greater probability of interactions than with other regimens.</li> </ul>	

Table 2 (Continued)

Third drug	Regimen <sup>a</sup>	Remarks <sup>b</sup>
	ABC/3TC+LPV/r	- Avoid in patients with hyperlipidemia and/or high cardiovascular risk. - ABC is contraindicated in patients with a positive HLA-B5701 test result. When ABC is prescribed, all possible measures should be taken to minimize modifiable cardiovascular risk factors. - Greater probability of interactions than with other regimens.
	3TC+LPV/r	- Avoid in patients with hyperlipidemia and/or high cardiovascular risk. - Can be used as an alternative to conventional triple therapy when neither TDF nor ABC can be prescribed. - Greater probability of interactions than with other regimens.
	RAL+DRV/r	- Do not use in patients with CD4 <200 cells/ $\mu$ L. - Avoid in patients with PVL >100,000 copies/mL. - Can be used as an alternative to conventional triple therapy when neither TDF nor ABC can be prescribed. - Greater probability of interactions than with other regimens.
	RAL+LPV/r	- Avoid in patients with hyperlipidemia and/or high cardiovascular risk. - Do not use in patients with CD4 <200 cells/ $\mu$ L. - Avoid in patients with PVL >100,000 copies/mL. - Can be used as an alternative to conventional triple therapy when neither TDF nor ABC can be prescribed. - Greater probability of interactions than with other regimens.

The clinical trials on which the evidence for each regimen is based are referenced in the text.

In drugs from the same family and with the same level of recommendation, the order reflects the preference of the expert panel.

Cost and pricing of the therapeutic regimens are addressed elsewhere in these guidelines. The cost-effectiveness of the regimens is analyzed formally in an article published simultaneously with the guidelines.

<sup>a</sup> When available, fixed-dose combinations should be used. There are no data showing that FTC and 3TC can be considered therapeutically equivalent; therefore, use of one or other drug in the regimens selected essentially depends on experience of use in combination with other drugs in the regimen.

<sup>b</sup> The remarks reflect aspects that should be taken into consideration when choosing the regimen; they do not aim to be an exhaustive guide to the precautions to be taken when prescribing these drugs. Please see the main text and the appropriate Summary of Product Characteristics for more information.

<sup>c</sup> Use of cobicistat (COBI) to boost DRV or ATV has been approved by the EMA. However, at the time of writing, COBI is not marketed in Spain as a stand-alone drug. A single-tablet coformulation (DRV/COBI) has been approved, although it is not available in Spain.

- The combination RPV/TDF/FTC can be considered a preferred regimen in patients with a PVL <100,000 copies/mL (A-I).

### 3. PI/r

#### Recommendations

- The recommended PI-based regimens are DRV/r (or DRV/cobicistat [COBI]) QD+TDF/FTC and ATV/r (or ATV/COBI) QD+TDF/FTC (A-I). The combination of ATV/r (or ATV/COBI)+ABC/3TC is also recommended, although it should be avoided in patients with a PVL >100,000 copies/mL (A-I).
- Other PI-based regimens include LPV/r (BID or QD)+TDF/FTC or ABC/3TC (B-I). The combination DRV/r (or DRV/COBI)+ABC/3TC can also be used, although it has not been formally assessed in a clinical trial (B-III).
- ATV and DRV can be boosted interchangeably with ritonavir (RTV) 100 mg or COBI 150 mg (B-II).
- LPV/r+3TC, LPV/r+RAL, and DRV/r+RAL can be used as an alternative to conventional triple therapy when it is not possible to use TDF or ABC (B-I). NRTI-sparing double regimens (DRV/r or LPV/r+RAL) should not be used as initial treatment in patients with advanced disease (CD4+ T-lymphocyte counts <200 cells/ $\mu$ L and/or a PVL >100,000 copies/mL) (A-I).

### 4. INSTI

#### Recommendations

- DTG combined with TDF/FTC (A-I) or ABC/3TC (A-I), and RAL combined with TDF/FTC (A-I), are the preferred regimens in initial treatment.
- The combination EVG/COBI/TDF/FTC can be used as initial ART, although it should not be used in patients with an estimated glomerular filtration rate <70 mL/min) (A-I).
- The combination of RAL with ABC/3TC is considered an alternative in initial treatment because less evidence is available (A-I).

### Switching ART in patients with an undetectable PVL

PVL is considered undetectable at <50 copies/mL. Most clinical trials on switching ART included patients who have maintained virological suppression at this level for at least 6 months.

There are several reasons for changing an efficacious ART regimen (e.g., toxicity, comorbid conditions, drug interactions, and reducing the pill burden or number of daily doses). However, efficacious ART always has the common and priority objective of maintaining an undetectable PVL. Efficacious ART can be switched in two ways: proactively, which is recommended when attempting to prevent a severe or incurable adverse event, and reactively, which is mandatory in the case of an adverse effect.

After switching ART in this context, maintenance of virological suppression and performance of relevant laboratory tests should be evaluated within 3–6 weeks.

#### Virological considerations when switching efficacious ART

##### Recommendation

- Switching from a regimen containing 2 NRTI+PI/r to one containing 2 NRTI+1 NNRTI, RAL, EVG/COBI or unboosted ATV is only possible if the antiviral activity of the 2 NRTI and third drug can be guaranteed (A-I). Without forgetting that the main objective is to maintain virological suppression, the physician should carry out a meticulous evaluation of the toxicity profile, interactions, dietary restrictions, and anti-HBV activity (where necessary) of the new regimen.

#### Considerations on the grading of evidence with respect to switching efficacious ART

##### 1. Switching drugs from the same family

###### a) NRTI

Switching stavudine (d4T) or zidovudine (ZDV) for TDF or ABC

### Recommendation

- Proactive switch from d4T or ZDV to TDF or ABC in order to prevent or try to reverse lipoatrophy associated with thymidine analogs (A-I).

#### Switching from ABC/3TC to TDF/FTC Recommendation

- The association between ABC and increased incidence of cardiovascular events is open to debate. This committee cannot make a recommendation on the strength of evidence for switching from ABC/3TC to TDF/FTC.

#### Switching from TDF to ABC Recommendation

- The switch from TDF to ABC is a valid option in patients with osteopenia or osteoporosis associated with TDF, as long as the results of HLA-B\*5701 testing are negative (A-II).

#### b) NNRTI Switching from EFV/TDF/FTC to RPV/TDF/FTC Recommendation

- In patients with adverse central nervous system (CNS) effects caused by EFV/TDF/FTC, the switch to RPV/TDF/FTC is one of the options that can improve the symptoms associated with EFV (A-II). There are no data in favor of recommending a proactive switch in patients who do not have CNS symptoms or data comparing this switch with a switch to other antiretroviral drugs that do not cause CNS effects.

#### Switching from EFV to etravirine (ETR) Recommendation

- In patients with CNS adverse effects caused by EFV, the switch to ETR can lead to an improvement in EFV-associated neuropsychological symptoms (A-II). There are no data to recommend a proactive switch in patients who do not have CNS symptoms or data comparing this switch with a switch to other antiretroviral drugs that do not cause CNS effects.

#### Switching from EFV to NVP Recommendation

- In patients with CNS adverse effects caused by EFV, switching to NVP could improve EFV-associated neuropsychological symptoms (A-II). There are no data to recommend a proactive switch in patients who do not have CNS symptoms or data comparing this switch with a switch to other antiretroviral drugs that do not cause CNS effects.

#### Switching from EFV or NVP+2 NRTI to EFV/TDF/FTC Recommendation

- Switching to EFV/TDF/FTC is an option in patients taking ART with EFV and NVP who wish to reduce their pill burden (A-II).

#### c) Protease inhibitors Switching from ATV/r+ABC/3TC to unboosted ATV+ABC/3TC Recommendation

- In patients taking ATV/r+ABC/3TC, switching to ATV+ABC/3TC is a simplification option when attempting to avoid RTV, owing to

hyperbilirubinemia, dyslipidemia, diarrhea, or the risk of interactions with RTV (A-I).

#### Switching from ATV/r+TDF/FTC to unboosted ATV+ABC/3TC Recommendation

- In patients taking ATV/r+TDF/FTC, switching to ATV+ABC/3TC is an option in those cases where both TDF and RTV have to be avoided (A-II).

#### 2. Switching to antiretroviral drugs from a different family

##### a) Switching from NRTI to INSTI

#### Switching from TDF to RAL Recommendation

- Switching from TDF to RAL in patients who are also taking a PI/r is also an option in patients with reduced bone mineral density (A-II).

##### b) Switching from NNRTI to INSTI Switching from EFV to RAL Recommendation

- Switching from EFV to RAL is an option in patients with CNS adverse events caused by EFV (A-II). There are no data to recommend a proactive change in patients with no CNS symptoms or data or data comparing this switch with a switch to other antiretroviral drugs that do not cause CNS effects.
- Switching from EFV to RAL is a valid option in patients with dyslipidemia caused by EFV (A-I).

#### Switching from TDF/FTC+EFV or NVP to TDF/FTC/COBI/EVG Recommendation

- Switching from TDF/FTC+EFV or NVP to coformulated TDF/FTC/COB/EVG is virologically safe. This change is an option for patients who wish to simplify their current regimen and can improve CNS symptoms caused by EFV (A-I). There are no data to recommend a proactive change in patients who do not have CNS symptoms. Similarly, there are no data comparing this switch with switches to other drugs that do not cause CNS symptoms.

##### c) Switching from fusion inhibitors to INSTI Switching from enfuvirtide (ENF) to RAL Recommendation

- Switching from ENF to RAL is a safe option that obviates parenteral administration of enfuvirtide (A-I).

##### d) Switching from a PI to an NNRTI Switching from a PI/r to EFV/TDF/FTC Recommendation

- Switching to EFV/TDF/FTC is an option in patients who are taking ART with PI. This approach makes it possible to reduce the daily pill burden, although patients may experience EFV-induced CNS adverse effects (B-I).

#### Switching from PI/r to NVP Recommendation

- Switching from a PI to NVP could be an option in patients taking a PI/r in order to avoid the adverse effects of RTV (B-III).

### Switching from PI/r to RPV/TDF/FTC Recommendation

- Switching to an ART regimen comprising 2 NRTI and 1 PI/r to the co-formulation RPV/TDF/FTC is a valid option in patients with gastrointestinal disorders or dyslipidemia. It also enables the daily pill burden to be reduced (A-I).

### e) Switching from PI/r to INSTI Switching from PI/r to RAL Recommendation

- Switching to RAL+2 active NRTI is a valid option for patients with dyslipidemia taking ART with NRTI+1 PI/r (B-I).

### Switching from PI/r to TDF/FTC/COBI/EVG Recommendation

- Switching from TDF/FTC+ATV/r or DRV/r or LPV/r to TDF/FTC/COBI/EVG is virologically safe. This switch is an option for patients who wish to simplify their current regimen and can improve RTV-associated digestive symptoms in some patients (A-I).

### 3. Dual therapy with 3TC and ATV/r or LPV/r

#### Switching 2 NRTI and ATV/r or LPV/r to 3TC+ATV/r or 3TC+LPV/r Recommendation

- Switching from 2 NRTI+ATV/r or LPV/r to dual therapy with 3TC+ATV/r or 3TC+LPV/r is an option if the clinician wishes to avoid or prevent the adverse effects caused by NRTI. This option requires the patient to fulfill the following criteria: (1) no chronic hepatitis B; (2) PVL <50 copies/mL for at least 6 months; and (3) no mutations in the protease gene or previous virological failure to PI/r or 3TC (A-I).

### 4. Monotherapy with PI/r Recommendation

- Monotherapy with DRV/r once daily or LPV/r twice daily is a valid option for preventing adverse effects caused by NRTI if the patient fulfills the following criteria: (1) no chronic hepatitis B; (2) PVL <50 copies/mL for at least 6 months; (3) no mutations in the protease gene and no previous virological failure with PI (B-I).

## Failure of ART

### 1. Definitions

**Virological failure.** Two confirmed determinations of PVL >50 copies/mL 24 weeks after initiating ART.

**Transient rebound of low-level viremia (“blips”).** Isolated and transient increase in PVL (50–200 copies/mL) after virological suppression.

**Immunological failure.** Inability to reach an adequate CD4+ T-lymphocyte count despite maintaining a PVL <50 copies/mL.

### 2. Incidence and determinants of virological failure

The determinants of virological failure can be patient-dependent (adherence), drug-dependent (dosing errors, potency, inadequate plasma concentrations, drug or food interactions), and HIV-dependent (pre-existing resistance mutations to any of the drugs in the current ART regimen).

### 3. Objective of ART after virological failure

The objective of ART is to achieve maintained viral suppression. Therefore, a new regimen should be started with 3 or at least 2 active antiretroviral drugs. Rescue ART should not be delayed in order to prevent the accumulation of resistance mutations and increased PVL.

### 4. Strategies for improving the success of rescue ART regimens

The measures to be taken when prescribing rescue ART are as follows: facilitating adherence, determining resistance mutations and viral tropism, reviewing previous therapy, and occasional monitoring of plasma concentrations of antiretroviral drugs.

### 5. Clinical scenarios in virological failure

#### 5.1. Virological failure with low viral loads

- PVL between 50 and 200 copies/mL. It is generally not recommended to modify ART, although some studies have demonstrated selection of new resistance mutations and an association between bacterial translocation and systemic inflammation.
- PVL between 200 and 1000 copies/mL. This level is associated with selection of resistance mutations. Intensification of ART by adding a single active drug is contraindicated in these situations.

#### 5.2. Early virological failure

Early virological failure occurs after the first line of ART. Selection of resistance mutations and second-line regimens differ according to the initial ART regimen applied.

- Virological failure to 2 NRTI+NNRTI: The most common resistance mutations after virological failure with EFV or NVP are K103N, L100I, and Y181C. K103N alone maintains sensitivity to RPV and ETR. Virological failure with RPV leads to selection of E138K and/or Y181C, which generate resistance to all the NNRTI. Virological failure to NNRTI may be accompanied by resistance mutations to NRTI, especially that caused by M184V and, albeit less frequently, K65R.
- Virological failure to 2 NRTI+PI/r: The probability of resistance to PI is very low. PI/r protect against resistance to NRTI, which is uncommon. The only mutation involved is M184V.
- Virological failure to 2 NNRTI+INSTI: Virological failure to RAL or EVG leads to cross-resistance between both drugs. The mutations involved are T66K, E92Q, Q148H/K/R, and N155H. In this setting resistance to NRTI is frequent. Clinical trials involving naïve patients have shown that DTG has a high genetic barrier, with the result that resistance mutations are very rarely detected in the integrase gene or reverse transcriptase gene after virological failure to DTG.

It is generally recommended to use a PI/r with two antiretroviral drugs, preferably NRTI, that conserve their antiviral activity. DRV/r is the most efficacious PI/r of all the rescue lines analyzed. In patients whose first NNRTI-based ART regimen (i.e., one based on NVP or EFV) fails, a dual regimen with LPV/r+RAL is not inferior to LPV/r+2 or 3 NRTI (SECOND LINE study).

#### 5.3. Advanced virological failure

Advanced rescue therapy is a rescue regimen that is administered when virological failure has occurred with at least 2 ART lines. A regimen comprising 3 or at least 2 active antiretroviral drugs can be designed by combining drugs from different families. In this

setting, DRV/r is superior to other PI/r, and DTG at 50 mg BID is efficacious in most patients with resistance to RAL and EVG.

#### 5.4. Virological failure in patients with no therapeutic options

In patients with no therapeutic options, it is impossible to design an ART regimen with a minimum of 2 fully active antiretroviral drugs. Most patients continue to have relatively stable CD4+ T-lymphocyte counts. ART should not be suspended. The ART regimen should be non-suppressive and easy to take, with minimum toxicity. It should also be able to reduce viral replicative capacity and not generate resistance mutations. Furthermore, the patient should be referred to a specialized center with experience in treating this population and where access to new antiretroviral drugs is provided through clinical trials or expanded-access studies.

Recommendations (switching ART because of virological failure)

- The objective of rescue ART is to achieve a PVL <50 copies/mL (A-II).
- Switching ART because of virological failure should be performed early to avoid accumulation of mutations and to facilitate the response to the new treatment (A-III).
- The new ART regimen should contain 3 totally active antiretroviral drugs. If this is not possible, 2 fully active drugs should be combined with other drugs that maintain partial virological activity, especially in the case of advanced rescue in patients with limited therapeutic options (A-I).
- Resistance and viral tropisms should be assessed in order to design the best alternative regimen. The test should be performed while the patient is receiving the failed treatment or as soon as possible after suspension of the failed treatment. If the results of previous genotyping tests are available, all the resistance mutations detected should be evaluated (A-I).
- The causes of virological failure—poor adherence, drug or food interactions, previous therapy, and previous toxicity—should be analyzed. The new regimen should be comfortable and well tolerated (A-III).
- In patients who have experienced virological failure, DRV/r is the PI/r that has proven most efficacious in all the rescue lines. When major resistance mutations are present, the recommended dose is 600/100 mg BID (A-I).
- DTG is the INSTI of choice in patients who experience virological failure who are INSTI-naïve (A-I). In the case of previous failure to RAL or EVG, the dose of DTG should be 50 mg BID, accompanied by optimized background therapy (A-II).
- The use of tipranavir/ritonavir (TPV/r), ENF, or thymidine analogs is restricted to patients with no other therapeutic options (A-III).
- In general, ART should not be modified in patients with low-grade virological failure (PVL, 50–200 copies/mL) who are receiving ART with a high genetic barrier. In patients with a PVL >200 copies/mL, genotyping should be performed at a reference laboratory. The choice of the new ART regimen should be based on both resistance mutations and previous ART. ART should not be intensified with a single drug (A-III).
- ART should not be suspended in patients with advanced virological failure and no therapeutic options (A-II). In this situation, the approach should involve antiretroviral drugs that reduce viral replicative capacity and do not lead to resistance mutations that might compromise future treatments (A-III).
- In patients with no therapeutic options, it is important to monitor the CD4+ count and PVL and to consult with clinicians and virologists specialized in resistance and rescue therapy who are involved in restricted access programs (B-III).

## Factors affecting the success of ART

### 1. Adherence

Adherence to ART is the patient's ability to become suitably involved in the choice, initiation, and completion of his/her treatment in order to achieve an undetectable PVL.

#### Recommendations

- Before initiating ART, the patient should be prepared and factors likely to limit adherence should be identified and corrected (A-III).
- Once ART has been initiated, a first check-up should be made after 2–4 weeks to verify adherence and correct adherence problems if necessary (A-III).
- Adherence should be monitored and reinforced at visits to the doctor (A-III).
- Adherence should be monitored by a multidisciplinary team including a doctor, nursing staff, specialists in psychological support, and a hospital pharmacist (AIII).
- In the case of patients whose adherence is irregular, it is preferable to use regimens based on PI/r (and probably DTG) in order to prevent the development of resistance (A-III). Despite the limited available clinical experience, preliminary data seem to indicate that DTG-based regimens can also prove useful in this type of patient (B-III).
- Using fixed dose combinations of antiretroviral drugs simplifies ART and thus facilitates continued adherence. The use of whole regimens in a single tablet is the most efficient strategy for preventing selective poor adherence (A-II).

### 2. Tolerability and adverse effects

Tolerability depends on drug-related factors (number and size of tablets, administration requirements, and number and intensity of immediate side effects) and patient related factors (age, sex, weight, clinical situation, and expectations from treatment).

#### a) Immediate adverse effects

The immediate adverse effects are well defined. In some cases, these can be anticipated and are usually easy to control. Adverse effects are usually gastrointestinal, cutaneous, or neuropsychological.

#### Recommendations

- Avoid the use of antiretroviral drugs whose immediate adverse effects are similar to clinical manifestations or laboratory abnormalities that are already present in a specific patient (A-II). HLA-B\*5701 testing is mandatory before prescribing ABC, since it has a positive predictive value of almost 100% for the risk of hypersensitivity reaction to this drug (A-I).
- The patient should be informed about the correct way to take an ART regimen and the possibility of immediate adverse events. In any case, the patient should be told how to deal with specific adverse events and always be able to contact the doctor directly. Mild immediate adverse events can be treated symptomatically by evaluating the patient's progress and tolerability. If the adverse effect is very intense or long-lasting or cannot be tolerated by the patient, the potential culprit antiretroviral drug(s) should be switched (A-I).

#### b) Late adverse effects

Late adverse effects are worse and more difficult to prevent and control. They exacerbate the symptoms of chronic diseases associated with aging and affect the functioning of organs and systems. In general, the absolute risk of late adverse effects of currently recommended antiretroviral drugs is very small.



## Recommendations

- ART should be tailored by evaluating the risk or presence of chronic diseases in such a way that the regimen selected does not contain antiretroviral drugs that can favor the onset or progression of these diseases (A-II).
- Withdrawal of some of the antiretroviral drugs involved in late adverse effects can improve—albeit partially—the underlying clinical abnormality, although it is not known whether such a modification can alter the natural history of the specific chronic disease or survival. Antiretroviral drugs contribute collaterally to the risk or progression of specific chronic diseases, although other factors are generally considered to be more important. Priority should be given to interventions to address these factors (A-II).

### 3. Drug interactions

Interactions between antiretroviral drugs or between antiretroviral drugs and other agents, food, or herbal products could have significant clinical consequences.

#### Recommendations

- All medications, natural products, and alternative medicines taken by the patient should be recorded in the clinical history in order to evaluate potential interactions (A-III).
- Contraindications should be taken into account and the corresponding dose adjustments made where necessary (A-I).
- Plasma levels should be monitored when prescribing 2 or more drugs with potential pharmacokinetic interactions in order to avoid toxicity or lack of efficacy (A-II).

## Special situations

### 1. Acute HIV infection

In more than 50% of cases, acute HIV infection is characterized by self-limiting acute febrile syndrome similar to influenza or infectious mononucleosis. Acute infection (first 30 days) should not be confused with recent infection (patients diagnosed during the previous 6 months).

#### Recommendations

- ART should be recommended in all patients with acute HIV infection, regardless of the symptoms, their severity, or their duration (A-II) and should be started as soon as possible to obtain the maximum benefit.
- ART should generally be offered to all recently infected patients (B-II). In patients with  $<500$  CD4+ T lymphocytes/ $\mu\text{L}$ , ART should be started during the first 4 months to obtain the maximum benefit.
- ART should be initiated in all cases where there is a high risk of transmission of HIV (A-II).
- ART should be initiated when acute HIV infection is detected during pregnancy (A-I).
- If ART is to be initiated, it should be done so with the same preferential regimens used to treat chronic HIV infection (A-I) (Table 2). A regimen comprising 2 NRTI and an INSTI could reduce PVL more rapidly during the first 4–8 weeks than PI or NNRTI and, thus, make it easier to reduce transmission of HIV (A-I). The combination of RAL+2 NRTI (preferably TDF/FTC) would also have the advantage of reaching higher concentrations in genital tract secretions (B-III).
- Testing for resistance and viral tropism should always be performed at diagnosis of acute or recent infection, irrespective of whether ART is to be initiated (A-II).

- If the results of resistance testing are not available, it is preferable to begin with a regimen based on a PI/r until the results become available (A-II).
- If is ART is initiated, it should be administered indefinitely (A-I).

### 2. Infection by HIV-2

The genomic organization of HIV-2 is similar to that of HIV-1, except for certain structural differences that can significantly affect its pathogenicity and its sensitivity to antiretroviral drugs.

#### Recommendations

- The general principles of ART in patients infected by HIV-2 should be the same as those of HIV-1 infection (A-III).
- The preferred regimen for initial ART in these patients is the combination of 2 NRTI and 1 PI/r (A-III).
- The use of NNRTI, MVC, or ENF is contraindicated for the treatment of HIV-2 infection (A-I).

### 3. Pregnancy

A specific GESIDA document and documents from other scientific societies on women and pregnancy are available. The most important recommendations are summarized below.

#### Recommendations

- All pregnant women must undergo HIV serology testing (AI). If the result is negative, testing must be repeated during the third trimester (A-II).
- Pre-pregnancy counseling must form part of health care for HIV-infected women of childbearing age (A-II).
- ART is indicated in all pregnant women, irrespective of CD4+ T-lymphocyte count and PVL, in order to ensure that PVL remains undetectable (A-I).
- The choice of specific antiretroviral drugs should be based on resistance studies, drug safety, and ease of adherence. If there are no resistance mutations, the regimen of choice is ZDV or TDF or ABC+3TC or FTC+LPV/r (A-I); if resistance mutations are detected, patients can receive any of the “preferential” and “alternative” antiretroviral drugs after a personalized evaluation (A-III).
- Intrapartum intravenous administration of ZDV is indicated in women whose PVL is  $>1000$  copies/mL or unknown at the time of delivery, irrespective of any previous ART received (A-I).
- Elective cesarean delivery is indicated at week 38 in women with a pre-labor PVL of  $>1000$  copies/mL (A-II).
- Mothers cannot breastfeed. Adapted formula food must be used (A-I).

### 4. Comorbid conditions

a) Initial ART in patients with opportunistic infections other than tuberculosis

#### Recommendations

- ART should be started within the first 15–30 days of treatment of the opportunistic infection (A-II).
- In patients with cryptococcal meningitis, it is prudent to wait several weeks before initiating ART (5 according to the largest study published to date, especially in patients with  $<5$  cells/ $\mu\text{L}$  in CSF) (A-I). Although a negative CSF culture supports initiation of ART (A-II), this approach should be taken into consideration when the antigen load begins to fall (B-III). Intracranial hypertension should be closely monitored (A-I).

## b) ART and tuberculosis

Treatment of tuberculosis in HIV-infected adults was the subject of a consensus document from GESIDA/Secretariat of the National AIDS Plan, which is available for consultation.

## Optimal timing of ART

## Recommendation

- ART should always be started during treatment of tuberculosis, irrespective of the CD4+ T-lymphocyte count, since it reduces the risk of death (A-I). The optimal time for initiating ART depends on the CD4+ T-lymphocyte count. If the CD4+ T-lymphocyte count is <50 cells/ $\mu$ L, ART should be started as soon as possible, after verifying tolerance to anti-tuberculosis treatment, but not later than the first 2 weeks (A-I). If the CD4+ T-lymphocyte count is >50 cells/ $\mu$ L, initiation of ART can be delayed until the intense phase of anti-tuberculosis treatment has been completed (8 weeks). This approach reduces the risk of adverse effects and the development of immune reconstitution inflammatory syndrome (IRIS) without compromising survival (A-I).

## ART regimens

Drug interactions constitute the main difficulty when attempting to treat tuberculosis and HIV infection simultaneously.

## Recommendations

- *Choice of NRTI.* No significant interactions or evidence of toxicity have been found between antituberculosis drugs and NRTI. Therefore, ABC, TDF, 3TC, and FTC can be used in these patients with no added risks (A-I).
- *Choice of the third drug.* Since most experience and the best results have been obtained with EFV, this is the antiretroviral drug of choice (A-I). The dose of EFV is standard for all patients (600 mg/day), irrespective of body weight and with no need to increase to 800 mg/day (A-I).
- *Alternative third drugs.* Based on experience or sufficient evidence, the alternative regimens that can be recommended include NVP at habitual doses (A-II) and RAL at 800 mg/12 h (A-II), although 400 mg/12 h has proven to be efficacious, as has MVC at 600 mg/12 h (A-III).
- *Drugs that cannot be used.* The other NNRTI (RPV and ETR), PI (whether boosted or not with RTV), and EVG should not be co-administered with rifampicin. In the exceptional case of a PI being the only option for ART, rifampicin should be replaced by rifabutin and the corresponding adjustment in drug doses should be made (A-II).

## Immune reconstitution inflammatory syndrome (IRIS)

IRIS is a frequent complication, especially in patients with a very low CD4+ T-lymphocyte count and when ART is initiated very early with respect to anti-tuberculosis treatment.

## Recommendations

- If the patient develops IRIS, neither ART nor anti-tuberculosis medication should be interrupted (A-III).
- The symptoms of IRIS can be managed by adding non-steroidal anti-inflammatory drugs in mild to moderate cases (A-III) or corticosteroids in moderate to severe forms (A-II).

## c) Renal insufficiency

For a complete overview of the diagnosis, prevention, and treatment of renal disorders in HIV-infected patients, please consult the ad hoc consensus document drafted by GESIDA, the SEN, and the SEQC.

## Recommendations

- It is necessary to adjust the dose of NRTI, except for ABC (A-II).
- No dose adjustment is required for NNRTI, PI, ENF, RAL, or DTG (A-II).
- The dose of MVC should be adjusted if it is used in combination with potent CYP3A4 inhibitors such as PI (except TPV/r), ketoconazole, itraconazole, clarithromycin, and telithromycin (A-II).
- Co-formulations of antiretroviral drugs are not advised in patients with significant renal insufficiency. In these cases, antiretroviral drugs should be administered separately and the appropriate adjustments made.
- In patients with renal insufficiency (any stage), kidney function should be closely monitored and nephrotoxic drugs avoided (A-III).
- In patients with advanced chronic renal insufficiency, the dose should be adjusted according to the recommendations of the summary of product characteristics, taking into account possible drug interactions, which are more common and more dangerous in this situation (A-II).

## d) Liver disease (HCV, HBV, cirrhosis)

## Initiation of ART

## Recommendations

- Patients co-infected with HCV should initiate ART irrespective of their CD4+ T lymphocyte count (A-II).
- In patients who require treatment for hepatitis C, it is generally preferable to initiate ART (A-III).
- Patients co-infected with HBV for whom treatment of HBV infection is indicated should initiate ART containing TDF (A-I).

## Choice of antiretroviral drugs

The choice of antiretroviral drugs must be made taking into account potential liver toxicity, presence of cirrhosis, HBV co-infection, and the need for simultaneous treatment of HCV.

## Recommendations

- Any antiretroviral drug can be used in patients with chronic liver disease and normal liver function, including patients with cirrhosis (Child–Pugh, class A) (A-I), although it seems reasonable to avoid dideoxynucleoside drugs (A-III).
- In patients with hepatocellular insufficiency, INSTI do not require dose adjustments (A-I). PI/r have a greater therapeutic margin than NNRTI (A-II).
- The combination of RVB with didanosine, d4T, or ZDV should be avoided (A-I).
- With the exception of sofosbuvir, available direct-acting antiviral drugs (telaprevir, boceprevir, simeprevir, and daclatasvir) present significant pharmacokinetic interactions with NNRTI and PI/r that require the dose to be adjusted or coadministration to be contraindicated (A-I).

## e) Cancer

Please refer to the relevant GESIDA documents for complete information on cancer in HIV-infected patients.

## Recommendations

- ART is an essential component of the treatment of HIV-infected patients with Kaposi sarcoma or non-Hodgkin lymphoma (A-II).
- Patients with other types of cancer who are not receiving ART should initiate therapy as soon as possible (A-II).

- Given its pharmacological characteristics, excellent tolerance, and minimal interactions, RAL should be the antiretroviral drug of choice, where possible, in patients receiving chemotherapy (A-III).

### Conflicts of interest

Koldo Aguirrebengoa has acted as a consultant for AbbVie, Gilead Sciences, and Janssen. He has participated in clinical studies and trials carried out by AbbVie, Merck Sharp & Dohme, Gilead, Janssen, and ViiV Healthcare and has received payment for talks from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, and ViiV Healthcare.

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Rosa Polo declares that she has no conflicts of interest.

Joaquín Portilla has acted as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, and ViiV Healthcare and has received clinical research grant support from AbbVie, Janssen, Merck Sharp & Dohme, and ViiV Healthcare. He has also received payment for talks from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV Healthcare.

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José Sanz Moreno has participated in clinical trials sponsored by Bristol-Myers Squibb, and ViiV Healthcare. He has received payment for consultancy work and preparing training presentations for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, and ViiV Healthcare.

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