Antiretroviral Resistance Guidelines

Update 2020

Spanish HIV/AIDS Research Network (RIS)
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Spanish HIV/AIDS Research Network

GOBIERNO DE ESPAÑA · MINISTERIO DE CIENCIA E INNOVACIÓN · Instituto de Salud Carlos III

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"Una manera de hacer Europa"

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Introduction

Antiretroviral resistance (ARV) testing continues to be a basic tool for monitoring HIV-infected patients allowing the selection of the optimal treatment. The approval of new drugs, the use of different therapeutic combinations and the identification of new mutations, makes necessary a constant revision of the interpretation of the new patterns of genotypic resistance to ARVs. In this respect, European and American institutions such as ANRS, geno2pheno, IAS-USA, Standford and Rega, propose different interpretation algorithms to determine the degree of resistance to ARVs.

This document represents an update of the Spanish "Antiretroviral Resistance Guidelines: update 2020", taking into account the latest data available for the interpretation of resistance to the most used drugs for the treatment of HIV infection including the latest incorporations to the drug pipeline. In order to be a practical and useful guide to be used in clinical practice, the interpretation of drug resistance is presented in tables by families of drugs. They indicate mutations or combinations of mutations associated with high-level resistance or intermediate resistance to each drug. The document is accompanied by the most relevant references on this topic.

Among the novelties, this year the Drug Resistance Interpretation RIS algorithm is available in an App for mobile and PDA devices. This App is freely available at Apple Store (Ris Algoritmo resistencias VIH) and Google Play (RIS Guía de Resistencia a los Antirretrovirales) and after an easy register process will be read to use in your mobile devices.

When to perform a HIV Drug Resistance Testing?

In all newly HIV diagnosed patients and in patients naïve to ARVs, a baseline genotypic resistance testing to reverse transcriptase (RT) and protease (PR) in plasma is recommended. However, drug resistance test results must be known before starting treatment, only when a combination of drugs including an NNRTI is considered as initial therapy. Taking into account the combinations currently recommended for the initiation of antiretroviral treatment (ART) in our environment, we can say that in most situations, ART initiation will not be conditioned by a baseline HIV drug resistance testing. Therefore, a 3-drugs ART combination including a boosted PR inhibitor (PI) or an INI (e.g. Dolutegravir or Bictegravir with high genetic barrier to resistance), could be initiated without having the baseline drug resistance test results. However, it is recommended that the results of the drug resistance test are available in the case of starting treatment with DTG + 3TC. However, the current data from the CoRIS cohort (prior to the implementation of the PreP in our country) showed a very low prevalence of the pre-treatment M184IV mutation, which would support the idea of start DTG + 3TC without waiting for the baseline resistance study report but the results should be reviewed as soon as it would be available to avoid monotherapy with DTG. It will be necessary additional evidence to support this statement.

With the data available describing a low prevalence of transmission of resistance mutations to INI, a resistance testing for integrase resistance (IN) in naïve patients is not recommended, unless mutations to more than one drug family were identified or if in the clinical history of the index case an exposure and failure to INI was indicated. In the case of patients with virological failure (confirmed HIV-RNA > 50 cop/mL), it is necessary to perform a genotypic resistance testing in plasma to design the most appropriate ART, including a resistance testing at the IN if the patient has received drugs from this family, and also a viral tropism genotypic test, if the future regimen includes Maraviroc, except if there is a previous tropism results not CCR5. In patients with undetectable viral load or with low viremia (HIV-RNA between 50-200 cop/mL) it would be possible to perform resistance and viral tropism testing in proviral DNA to guide a new ART if necessary (i.e. adverse effects, intolerance),

especially in patients with a history of resistance to ARV. These results could be of help but they are not clinically validated. In addition, if available, historical resistance genotypes should be reviewed in these cases, and the accumulated mutations should be considered when designing the new ART regimen.

	Interpretation of Resistance to NRTI			
Drug	**AZT**	**ABC**	**TDF/TAF****	**3TC/FTC*****
Resistance	T215Y/F	K65R	K65R	M184I/V
	Q151L/M (complex) Codon 69 insertion ≥3 TAM	Q151L/M (complex) Codon 69 insertion ≥3 TAM	Codon 69 insertion ≥ 4 TAM	Codon 69 insertion
Intermediate Resistance	< 3 TAM	K70E/G L74I/V Y115F M184V < 3 TAM	K65E/N K70E/G Q151L/M (complex) 3 TAM	K65R Q151L/M (complex)
Hypersusceptibility*	**K65R** **K70E/G** **M184I/V** **K65R+M184I/V**		**M184I/V**	

AZT: Zidovudine; ABC: Abacavir; TDF/TAF: Tenofovir/ Tenofovir Alafenamide; 3TC: Lamivudine; FTC: Emtricitabine.

TAM: M41L, D67N, K70R, L210W, T215F/Y, K219Q/E.
Q151L/M complex: A62V, V75I, F77L, F116Y, Q151L/M.

*The presence of mutations that confer hypersusceptibility (green) with mutations that confer resistance would be interpreted as intermediate resistance, with the exception of K65R+M184I/V, which would reverse resistance to AZT. In the case of TDF, the presence of M184I/V will produce hypersusceptibility in combination with TAM and in absence of K65R.

**Although it has been described *in vitro* differences for the IC50 between TDF and TAF and their activity against some specific mutations, considering the current data obtained form the clinical trials, this panel recommends the same interpretation for both drugs.

***In case that an ARV failure containing 3TC or FTC is reported in the clinical history, then, 3TC or FTC should be considered as non-active drugs.

	Interpretation of Resistance to NNRTI				
Drug	**NVP**	**EFV**	**ETR**	**RPV**	**DOR**
Resistance	L100I K101P K103H/N/S/T V106A/M Y181C/I/V Y188C/H/L G190A/C/E/Q/S/T/V F227C/L M230L	L100I K101P K103N/S/T V106A/M Y181C/I/V Y188C/H/L G190A/C/E/Q/S/T/V F227C/L M230L	K101P Y181C/I/V ≥3(L100I,K101E/H//P,V106I, G190A/S, M230L)	L100I K101P E138K Y181C/I/V Y188L F227C M230I/L/V	V106A Y188L M230L F227L G190E
Intermediate Resistance	A98G K101E H221Y P225H	P225H	L100I 2 (K101E/H/P, V106I, G190A/S) Y188L M230L F227C	K101E E138A V179L H221Y	L100I+K103N V106M G190S P225H L234I

NVP: Nevirapine; EFV: Efavirenz; ETR: Etravirine; RPV: Rilpivirine; DOR: Doravirine.

	Interpretation of Resistance to PI		
Drug	**LPV/RTV**	**ATV/RTV**	**DRV/b*** **
Resistance	**I47A** **L76V** **V82A/F/S/T** **I50V+I84V** **≥4** (L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, G48V/M, **I50V**, F53L, I54M/L/T/V/A, L63P, A71I/L/V/T, G73S, **I84V**, L90M)	**I50L** **I84V** **N88S** **≥3** (L10F/I/R/V, G16E, K20M/R/I/T/V, L24I, V32I, L33F/I/V, M46I/L, I47V, G48V/M F53L, I54V/T/A/L/M, D60E, A71V/T, G73C/S/T/A, V82A/F/S/T, I85V, L90M)	**≥4** (V11I, V32I, L33F, I47V/A, **I50V**, **I54L/M**, T74P, **L76V**, V82F, **I84V**, L89V)* ≥**3(I50V**,**I54L/M**, **L76V**, **I84V**)*
Intermediate Resistance	**I50V** **I84V** **3** (L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, G48V/M, I50V, F53L, I54M/L/T/V/A, L63P, A71I/L/V/T, G73S, I84V, L90M) **I50L**	**2** (L10F/I/R/V, G16E, K20M/R/I/T/V, L24I, V32I, L33F/I/V, M46I/L, I47V, G48V/M F53L, I54V/T/A/L/M, D60E, A71V/T, G73C/S/T/A, V82A/F/S/T, I85V, L90M)	**3** (V11I, V32I, L33F, I47V/A, **I50V**, **I54L/M**, T74P, **L76V**, V82F, **I84V**, L89V)
Hypersusceptibility**		**L76V**	**I50L** **N88S**

LPV: Lopinavir; ATV: Atazanavir; DRV: Darunavir; RTV: Ritonavir.

* Considering the 800 mg every 24 hours dosage, the number of mutations to consider DRV resistance is ≥2 or one of those highlighted in bold (I50V, I54L/M, L76V, o I84V). In this context, 600/100 mg every 12 hours dosage must be considered, which refers to the pattern of mutations that appears in the table.

** The presence of mutations that confer hypersusceptibility (green) with mutations that confer resistance would be interpreted as intermediate resistance.

***DRV/b: Darunavir boosted with ritonavir or cobicistat.

	Interpretation of Resistance to INI			
Drug	**RAL**	**EVG**	**DTG**	**BIC***
Resistance	T66K E92Q/V Y143C/H/R Q148H/K/R N155H	T66A/K/I E92GQV S147G Q148H/K/R N155H R263K	Q148 H/K/R+ ≥2 G140A/C/S, E138A/K/T o L74I	[G140A/S+Q148H/K]+E138K or + (L74M and T97A)
Intermediate Resistance	H51Y T66A/I E92G E138A/K G140A/C/S G163R S230R R263K G118R F121Y	H51Y E138A/K G140A/C/S G163R S230R G118R F121Y	Q148 H/K/R+ G140A/C/S, E138A/K/T o L74I R263K	[G140S+Q148H]+ E138A or T97A [G140A/C+Q148R]+E138K or L74M G140S+Q148R R263K

RAL: Raltegravir; EVG: Elvitegravir; DTG: Dolutegravir; BIC: Bictegravir.
* Considering the current data available, this panel considers that for clinical practice DTG and BIC must be considered as drugs with a similar resistance profile. There are *in vitro* data suggesting a higher susceptibility for BIC than for DTG in presence of G140S+Q148R mutations.

Interpretation of Resistance to CCR5 antagonists

In most cases, resistance to CCR5 antagonists (Maraviroc) is caused by changes in the use of the coreceptor that HIV isolates use to infect target cells, as they emerge as a preexisting X4 tropism isolates as a minority population at the baseline and that they are below the limit of detection of the assay.

A genotypic determination of HIV-1 tropism should be made by analyzing the V3 region of the viral envelope before initiating treatment with a CCR5 antagonist and in the case of virological failure. The tropism results must be clear, therefore, the results must be reporting as CCR5-tropism, or CXCR4-tropism. If CXCR4-tropism isolates are detected in a patient, the tropism test should not be repeated in future failures, since treatment with a CCR5 antagonists is not recommended.

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Annex 1. Amino acids abbreviations:

A (Alanine)
C (Cysteine)
D (Aspartic acid)
E (Glutamic acid)
F (Phenilalanine)
G (Glycine)
H (Histidine)
I (Isoleucine)
K (Lysine)
L (Leucine)
M (Methionine)
N (Asparagine)
P (Proline)
Q (Glutamine)
R (Arginine)
S (Serine)
T (Threonine)
V (Valine)
W (Tryptophan)
Y (Tyrosine)