

Indicaciones del test de resistencias

	IAS-USA ^[1]	DHHS ^[2]	European ^[3]
Primary/acute	Recommend	Recommend	Recommend
Postexposure prophylaxis	—	—	Recommend
Chronic, Rx naive	Recommend*	Recommend	Strongly consider*
Failure	Recommend [†]	Recommend	Recommend
Pregnancy	Recommend	—	Recommend
Pediatric	—	—	Recommend

*If prevalence of drug resistance in untreated patients $\geq 5\%$ (European: $\geq 10\%$); should be considered if the prevalence is unknown or if exposure to someone receiving antiretroviral drugs is likely.

[†]Resistance testing should also be considered if the HIV VL suppression achieved with a new antiretroviral regimen is not optimal.

1. Hammer SM, et al. JAMA. 2006;296:827-843.

2. DHHS guidelines, May 2006. Available at: <http://aidsinfo.nih.gov>.

3. Vandamme AM, et al. Antivir Ther. 2004;9:829-848.

SITUACION GLOBAL DE LAS RESISTENCIAS

1-. Resistencias en pacientes pretratados

2-. Problemas que nos encontramos en la determinación de resistencias:

- Resistencias en poblaciones minoritarias**
- Pacientes con fracaso con CV bajas**

3-. Utilización del genotipo para conocer el tropismo viral

Virological Failures with Resistance Through 2007

ARV Rx	M	Followup RT Sequence
EFV-CBV	12	69AT,98S,102Q, <u>103N</u> ,207E, <u>210FL</u> , <u>221HY</u>
EFV-CBV	7	<u>103N</u> ,106I,118IV,122P,162Y,176K, 200AT,202V,214L,224D
EFV-CBV	28	<u>90I</u> ,98S,102R, <u>103N</u> ,122E,135T,162F, <u>184V</u> ,200A,207G,211KR, <u>225H</u>
EFV-CBV	8	35T,60I, <u>70KR</u> ,83KR, <u>103N</u> , <u>108IV</u> ,135T, 175H,178IM, <u>184V</u> ,211KR, <u>215ST</u>
EFV-CBV	20	103N,135T,142V,162A,165L,169D,177E, <u>184V</u> , <u>188L</u> ,202V
EFV-Tr	45	<u>65R</u> , <u>68G</u> , <u>74I</u> ,83K, <u>100I</u> , <u>103N</u> ,165I,178L, <u>184V</u> ,207E,211K
EFV-Tr	11	60I,83K, <u>103N</u> ,135T,162A,165I,196E, 211G
EFV-Tr	12	<u>69N</u> , <u>90I</u> ,101E,121H,122E,135T,174E, 177E, <u>181CY</u> , <u>184V</u> , <u>190S</u> ,195L
EFV-T3	4	83K, <u>101KQ</u> , <u>138K</u> ,179GV, <u>184V</u> , <u>190E</u> , 196EK,200A

EFV-T3	50V, <u>103N</u> ,142V,165I,177E, <u>190A</u> ,200E, 211K
EFV-Ep	11KR,60I, <u>101Q</u> , <u>103N</u> ,122E,135T,178M, <u>184V</u> ,207E,211K
EFV-Triz	20R, <u>103KN</u> ,165I,178IM,196E,200A, 204Q,207D,211K
EFV-T3-ABC	48T,102R, <u>103N</u> ,173E,177E,G196E, T200A,R211G,F214L
NVP-Ep	49R, <u>62V</u> , <u>65R</u> , <u>115FY</u> ,135IT, <u>181C</u> , <u>184V</u> , 200AT,207E,211RS, <u>228QR</u>
LPVr-CBV	5V,60I,83K,90IV,142V,163T,165L,169D, <u>184V</u> ,200A,211K,214L
NFV-CBV	122R,166KR,179I, <u>184V</u> ,200A,202 207E,211K
NFV-CBV	49R,122KT,177E, <u>184V</u> ,214L
Triz	122E,123DG,165I,169D,178IL, <u>184V</u> , 200IT,202IV,214L,245I,250E

NRTI (n=12): 184V (9), 65R (2), 74V/I (1), 115F (1), 70R (1), 215S (1)

NNRTI (n=13) : 103N (9), 181C (2), 190A/S/E (3), 188L (1)

CBV: AZT/3TC, Tr: TDF/FTC, T3: TDF/3TC
Triz: ZDV/3TC/ABC, Ep: ABC/3TC

Fessel WJ et al. Low Risk of Initial ART Failure in Patients with Wild Type HIV-1 by Standard Genotypic Resistance Testing. CROI 2008

Potential Explanation for Infrequent Resistance During First Line Therapy

- Low rate of resistance during first line therapy is due to “robust” regimens
 - Higher genetic barrier to resistance
 - Drugs with similarly long half-lives
- Drugs are generally well tolerated and patients are able to change regimens.
 - Changes from EFV to NVP or ATV/r and from ATV/r to NVP or EFV are common.
- Early detection of virological failure appears unlikely to be the

explanation for infrequent drug resistance
Fessel, et al. Low Risk of Drug Resistance in Patients with Wild Type HIV-1 by Standard Genotypic Resistance Testing. CROI 2008

Resistencias en pacientes pretratados

-Primera línea:

- La selección de fármacos con alta barrera genética disminuye el riesgo de seleccionar resistencias (IP/r)
 - ¿Más recomendables en pacientes con clara probabilidad de no correcta adherencia?
- El cambio de tratamiento tras el fracaso debe ser lo más precoz posible para evitar la acumulación de resistencias
(a pesar de que el fracaso sea con baja replicación!!)

Resistencias en pacientes pretratados

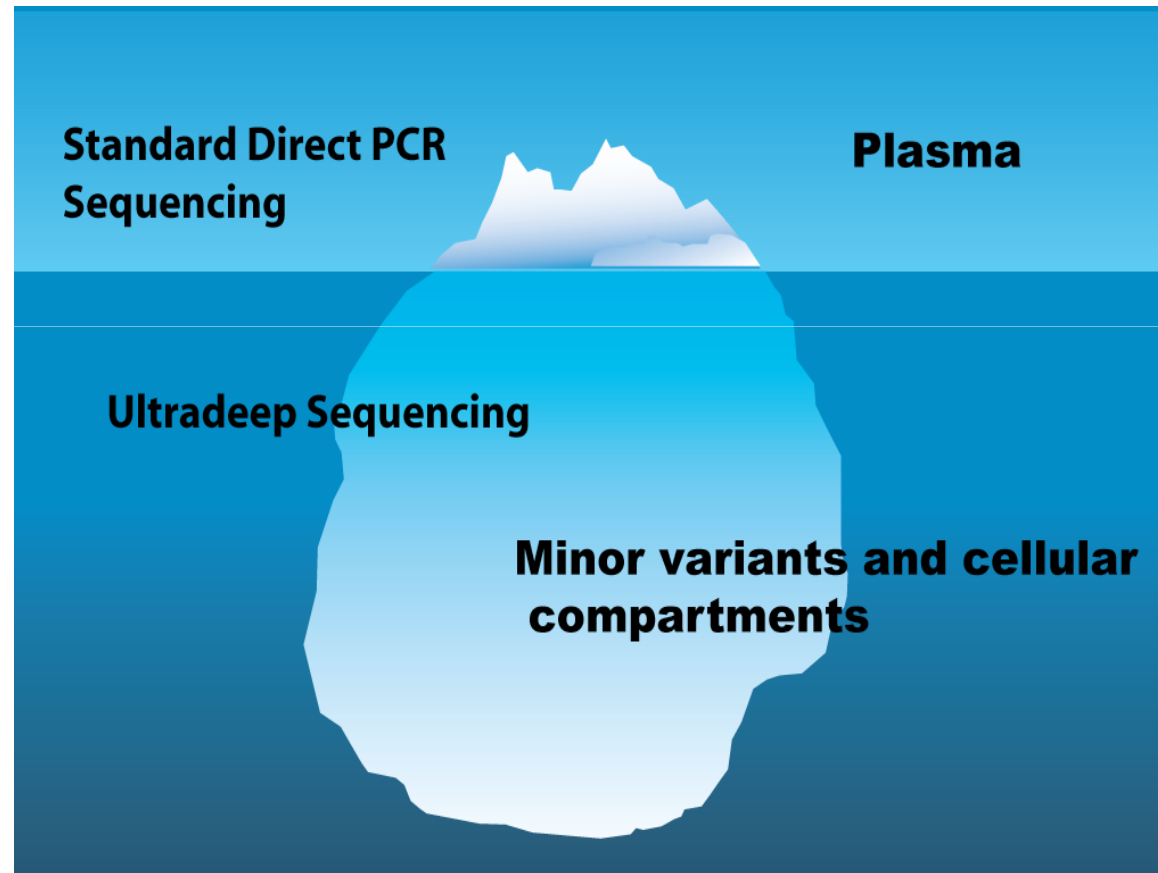
- Tratamiento de rescate:

- En el tratamiento de rescate hay que considerar el sumatorio de todas las mutaciones de los genotipados previos y las posibles mutaciones que puedan estar “ocultas” tras fracasos previos.
- El tratamiento de rescate debe incluir al menos 2 fármacos con actividad plena, si no es posible valorar otras opciones.

Problemas que nos encontramos en la determinación de resistencias

- Resistencias en poblaciones minoritarias
- Pacientes con fracaso con CV bajas

Standard Sanger Sequencing Detects the Most Common Circulating HIV-1 Variants



HIV-1 Quasispecies: Distribution of Genetic Variants

	1									99
f1.pep	-----i	--v--i-	-----	-----	-----l	-----	-----p	-----v	---i--	-----d
f10.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f3.pep	-----i	--v-----	-----	a	-----l	-----	-----p	-----v	---i--	-a---d-
f4.pep	-----i	--v--i-	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f5.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f510a.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f51a.pep	-----i	--v-----	-----	-----	-----l	l	-----p	-----v	---i--	-a---d-
f52a.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	t	---i--	-v---d-
f53a.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f54a.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f55a.pep	-----	--v-----	-----	-----	-----l	-----	-----p	t	---i--	-v---d-
f56a.pep	-----	f--v-l	-----	i	-----l	-----	-----p	t	---i--	-v---d-
f57.pep	-----	i--v-----	-----	-----	r-----l	-----	-----p	t	---i--	-v---d-
f57a.pep	-----	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f58.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f58a.pep	-----	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f59a.pep	-----i	--v-----	-----	-----	*-----l	-----	-----p	-----v	---i--	-a---d-
f6.pep	-----i	--ve--i-	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f62a1.pep	-----i	--v-----	-----	-----	-----l	-----	-----p	t	---i--	-v---d-
f7.pep	-----	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
f8.pep	-----	--v-----	-----	-----	-----l	-----	-----p	-----v	---i--	-a---d-
Consensus	PQITLWQRPL	VTIKIGGQLK	EALLDTGADD	TVLEEMNLPG	RWKPKMIGGI	GGFIKVRQYD	QILIEICGHK	AIGTVLVGPT	PVNIIGRNLL	TQIGCTLNF

21 clones of HIV-1 protease from the plasma of a heavily treated patient

Minority Variants: Implications for 2nd Generation NNRTIs: **Acquired** NNRTI Resistance

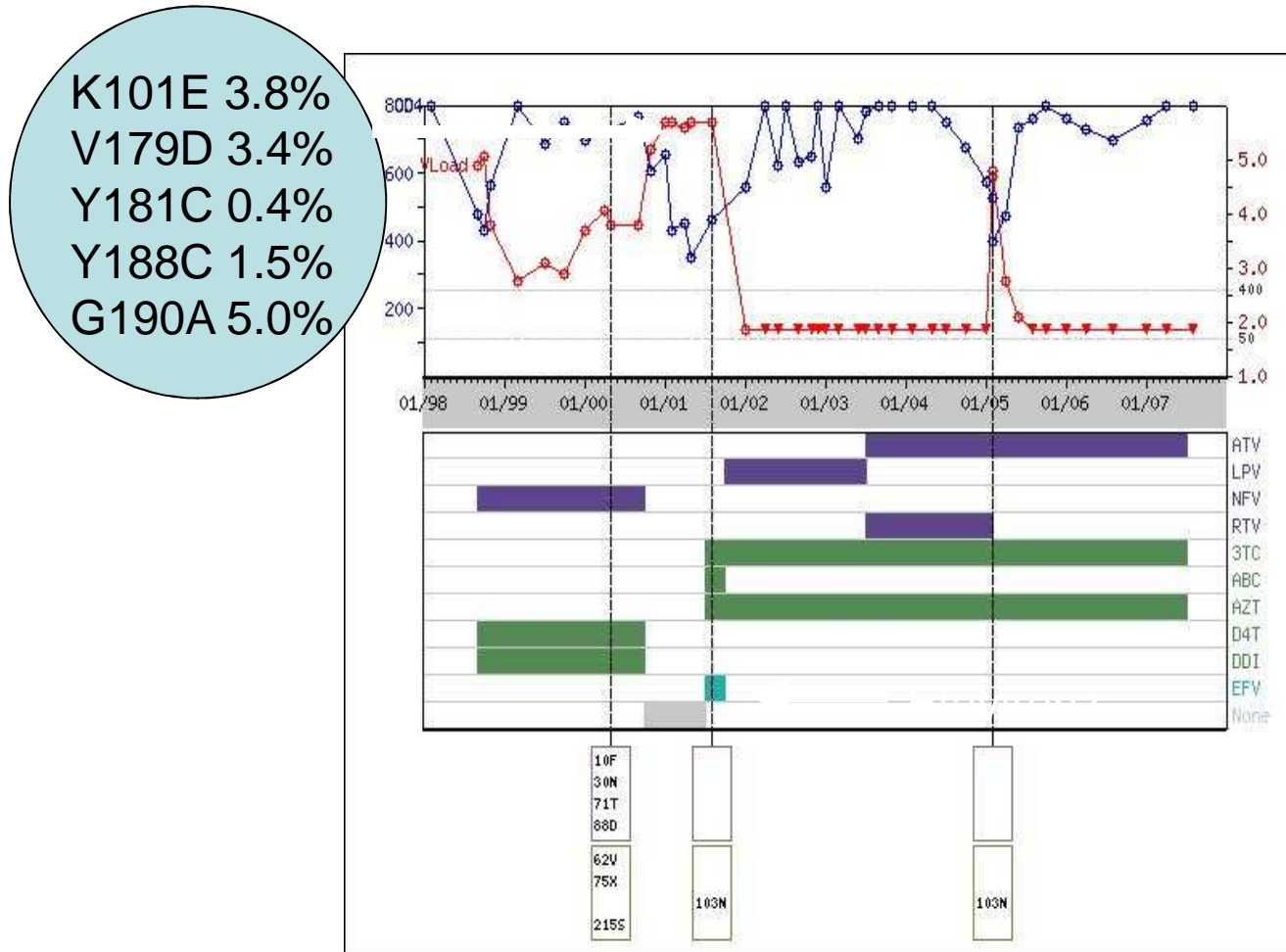
TABLE 2. Clinical Characteristics and UDPS Results in 20 NNRTI-Treated Patients With Plasma Samples Containing the RT Mutation K103N

PID	CD4 Count, NNRTI	HIV-1 RNA, Cells/ μ L	Log Copies/mL	Mutations Detected by Direct PCR Sequencing	Mutations Detected Only by UDPS	ETR Mutations†	Other NNRTI Mutations
6584	EFV	464	5.7	103NK , 118IV, 123E, 165IT, 174E, 214L	90I*(8.2), 101E*(3.8), 101N(2.4), 104N(3.1), 179D*(3.4), 188C(1.5), 189I(2.3), 190A*(4.9)	2 (2)	2
6455	EFV	463	4.5	74LV , 101R, 102Q, 103N , 135V, 142V, 162A, 174H, 184V , 211K, 221HY , 234I/L	20R(13), 65R(9.7), 67N(2.4), 75I(14), 100I*(32), 108I(4.8), 190A*(5.4), 219N(2.7), 224V(5.8), 225H(11.2), 228R(5.0)	2	2
1872	NVP	239	4.5	20R, 41L , 42AE, 43KN, 64KR, 103N , 122E, 169D, 179I, 184MV , 215Y	36D(18), 181C*(3.5), 190A*(3.2), 196E(6.1), 210W(6.3), 237N(5.9)	2	0
26423	EFV	27	5.7	35I, 75LV, 103N , 121Y, 122E, 135T, 176S, 200E, 211K, 225HP	62V(1.4), 69N(1.1), 74V(8.5), 101E*(4.0), 106I*(1.0), 190S*(4.8), H221Y(1.1)	2 (1)	1
1838	DLV	91	4.9	20R, 35MI, 67N , 102Q, 103N , 122E, 162C, 184V , 200A, 203K, 207E, 210W , 211K, 215Y , 223E	6K(8.6), 53K(2.0), 74V(12), 83K(58), 108I(28), 111I(3.5), 118I(73), 181C*(7.0), 219E(7.9), 236L(1.2)	1	2
5248	EFV	120	5.3	103N , 122E, 184V , 207E, 225H	6K(2.7), 74V(13), 100I*(14), 108I(2.3), 219E(1.1)	1	1
8350	EFV	261	4.5	41L, 101KQ, 103N , 108IV , 122E, 135T, 142V, 166R, 207E, 215V	184V(1.2), 190S*(3.1), T200A(8.5), 225H(1.2)	1	1

Varghese V et al. Minority variants associated with transmitted and acquired HIV-1 NRTIs: Implications for the use of 2nd generation NNRTIs. JAIDS 2009

Minority Variants: Implications for 2nd Generation NNRTIs

NNRTIs: **Acquired** NNRTI Resistance



Varghese V et al. Minority variants associated with transmitted and acquired HIV-1 NRTIs: Implications for the use of 2nd generation NNRTIs. JAIDS 2009

Utilización del genotipo para conocer el tropismo viral

Potential Genotypic Approaches to Predicting Coreceptor Tropism

- Standard direct PCR sequencing
 - Low sensitivity
- Standard direct PCR sequencing in triplicate
 - Has generated recent interest
- Ultra-deep Pyrosequencing
 - Probably competitive with Enhanced Sensitivity Tropism Assay
 - Complicated to perform