

**ANRS - AC 43: RESISTANCE GROUP
GENOTYPE INTERPRETATION: NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS**

	Mutations associated with resistance	Mutations associated with « possible resistance »
ZDV	<ul style="list-style-type: none"> • T215A/C/D/E/G/H/I/L/N/S/V/Y/F [1, 2, 3, 4] • At least 3 mutations among: M41L, D67N, K70R, L210W, K219Q/E [1, 2, 3, 4] • Q151M • Insertion at codon 69 	
3TC/FTC	<ul style="list-style-type: none"> • K65R [8, 9, 11] • M184V/I • Insertion at codon 69 	<ul style="list-style-type: none"> • Q151M
ABC	<ul style="list-style-type: none"> • At least 3 mutations among: M41L, D67N, M184V/I, L210W, T215A/C/D/E/G/H/I/L/N/S/V/Y/F [5, 20] • K65R [6, 8, 9, 24] • L74V/I [16, 17, 18, 19, 20, 24] • Y115F [24] • Q151M • Insertion at codon 69 	<ul style="list-style-type: none"> • 2 mutations among: M41L, D67N, L210W, T215A/C/D/E/G/H/I/L/N/S/V/Y/F [5, 20] • M184V/I [24]
TDF/TAF	<ul style="list-style-type: none"> • At least 4 mutations among: M41L, E44D, D67N, T69D/N/S, L74V/I, L210W, T215A/C/D/E/G/H/I/L/N/S/V/Y/F [10, 12, 21, 25, 26] • K65R/E/N [6, 7, 8, 9, 22, 23, 25, 26] • Insertion at codon 69 • K70E [13, 14, 15] 	<ul style="list-style-type: none"> • 3 mutations among: M41L, E44D, D67N, T69D/N/S, L74V/I, L210W, T215A/C/D/E/G/H/I/L/N/S/V/Y/F [10, 21, 25, 26]
ISL	<ul style="list-style-type: none"> • M184V/I [27, 28, 29] 	<ul style="list-style-type: none"> • A114S [29]

ZDV: zidovudine, 3TC: lamivudine, FTC: emtricitabine, ABC: abacavir, TDF: tenofovir disoproxil fumarate, TAF: tenofovir alafenamide, ISL: islatravir

For didanosine and stavudine refer to previous rules (See Archives, September 2017, version 27)

For DNA provirus, Impact of stop codons and G to A mutations on ARV resistance is unknown

**ANRS - AC 43: RESISTANCE GROUP
GENOTYPE INTERPRETATION: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

	Mutations associated with resistance	Mutations associated with « possible resistance »
EFV	<ul style="list-style-type: none"> • L100I • K101E • K103H/N/S/T [1] • V106M [2] • E138K [12, 13] • Y181C/I • Y188C/L • G190A/C/E/Q/S/T/V • P225H • M230L 	
NVP	<ul style="list-style-type: none"> • A98S (for HIV-1 subtype C only) [3] • L100I • K101E • K103H/N/S/T [1] • V106A/M [2] • Y181C/I • Y188C/H/L • G190A/C/E/Q/S/T/V • M230L 	<ul style="list-style-type: none"> • E138K [13]
ETR	<ul style="list-style-type: none"> • At least 3 among: V90I, A98G, L100I, K101E/H/I/P/R, V106I, V179D/F/I/L/M/T, G190A/S, M230L [4, 7, 8, 9, 10, 11] • E138K [12, 13] • Y181C/I/V [5, 6] • H221Y [12,16] 	<ul style="list-style-type: none"> • 2 mutations among: V90I, A98G, L100I, K101E/H/I/P/R, V106I, V179D/F/I/L/M/T, G190A/S, M230L [4, 7, 8, 9, 10, 11] • E138A/G/Q/R/S [5, 6, 7, 8]
RPV	<ul style="list-style-type: none"> • K101E/P [9, 13] • E138A/G/K/Q/R/S [12, 13, 14] • V179L [9] • Y181C/I/V [13] • Y188L [9] • F227C [9] • H221Y [13] • M230I/L/V [9] • L100I + K103N/S [9, 15] • L100I + K103R + V179D [15] 	<ul style="list-style-type: none"> • A98G [22]

DOR	<ul style="list-style-type: none">• V106A/M [17, 18, 19, 20 ,21]• Y188L• G190E/S [21]• M230L• L100I + K103N [17, 19]• K103N + Y181C• K103N + P225H• F227C [21]• At least 4 among: A98G, L100I, K101E, V106I, E138K, , Y181C/V, G190A or H221Y [23]	<ul style="list-style-type: none">• At least 2 among: A98G, L100I, K101E, V106I, E138K, Y181C/V, G190A or H221Y [23]
-----	--	--

EFV: efavirenz, NVP: nevirapine, ETR: etravirine, RPV : rilpivirine, DOR : doravirine.

For DNA provirus, Impact of stop codons and G to A mutations on ARV resistance is unknown

**ANRS - AC 43: RESISTANCE GROUP
GENOTYPE INTERPRETATION: PROTEASE INHIBITORS**

	Mutations associated with resistance	Mutations associated with « possible resistance »
LPV/r	<ul style="list-style-type: none"> At least 4 mutations among: L10F/I/R/V, K20M/R, L24I, L33F, M46I/L, I50V, F53L, I54M/L/T/V, L63P, A71I/L/V/T, V82A/F/S/T, I84V, L90M [1, 2, 3, 13] I47A [8, 9] L76V [11, 12] 	<ul style="list-style-type: none"> 3 mutations among: L10F/I/R/V, K20M/R, L24I, L33F, M46I/L, I50V, F53L, I54M/L/T/V, L63P, A71I/L/V/T, V82A/F/S/T, I84V, L90M [1, 2, 3, 13]
ATV/RTV 300/100 mg QD	<ul style="list-style-type: none"> I50L [4] N88S [20,21,22] At least 3 mutations among: L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, A71V/T, I84V, I85V, L90M [5, 7, 14, 23] 	<ul style="list-style-type: none"> 2 mutations among: L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, A71V/T, I84V, I85V, L90M [5, 7, 14, 23]
TPV/RTV 500/200 mg BID	<ul style="list-style-type: none"> At least a score of + 3*: M36I/L/V – F53L/W/Y + Q58E + H69I/K/N/Q/R/Y + L89I/M/R/T/V [6, 15] 	<ul style="list-style-type: none"> A score of + 2*: M36I/L/V – F53L/W/Y + Q58E + H69I/K/N/Q/R/Y + L89I/M/R/T/V [6, 15]
DRV/RTV** 600/100 mg BID 800/100 mg QD	<ul style="list-style-type: none"> At least 4 mutations among: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V [10, 16, 17, 18, 19] At least 2 mutations among: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V [10, 16, 17, 18, 19] 	<ul style="list-style-type: none"> 3 mutations among: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V [10, 16, 17, 18, 19]

LPV: lopinavir, ATV: atazanavir, TPV: tipranavir, DRV: darunavir, RTV: ritonavir

For indinavir, saquinavir, nelfinavir and fosamprenavir refer to previous rules (See Archives, September 2017, version 27)

* Insufficient data for HIV-1 subtype non-B

** Please note that rules are different for DRV/RTV 600/100 mg BID and 800/100 mg QD

For DNA provirus, Impact of stop codons and G to A mutations on ARV resistance is unknown

**ANRS - AC 43: RESISTANCE GROUP
GENOTYPE INTERPRETATION: FUSION INHIBITOR**

Mutations associated with resistance	
ENF T20	<ul style="list-style-type: none">• G36A/D/E/S/V [1, 2, 3, 4, 5, 6, 7]• V38A/E/K/M• Q40H/K/P/T• N42D/T• N43D/H/K/S• L44M• L45Q/M

ENF (T20): enfuvirtide

GENOTYPE INTERPRETATION: ATTACHMENT INHIBITOR

Mutations associated with “possible resistance” (gp120)	
FTR*	<ul style="list-style-type: none">• At least one mutation among: S375H/I/M/N/T, M426L/P, M434I/K, M475I [5]

FTR: fostemsavir

*HIV-1 CRF01_AE and HIV-1 group non-M strains are naturally resistant to Fostemsavir [1, 2, 3, 4]

ANRS - AC 43: RESISTANCE GROUP

GENOTYPE INTERPRETATION: INTEGRASE STRAND TRANSFER INHIBITORS

	Mutations associated with resistance	Mutations associated with « possible resistance »
RAL	<ul style="list-style-type: none"> • T66A/K [10, 40] • E92Q [1, 2] • G118R [10, 17] • F121Y [10,17] • G140A/S [7] • Y143A/C/G/H/R/S [1, 3, 4, 5, 8, 14] • N144D [42] • Q148E/G/H/K/R [1, 2] • V151L [9] • N155H/S/T [1, 2, 9] • E157Q [2] • S230R [18, 31, 32, 33] • R263K [16, 18] • L74 F/I + V75I [36] 	
EVG	<ul style="list-style-type: none"> • T66A/I/K [6] • E92Q [6] • T97A [19,20] • G118R [17] • F121Y [9,17] • E138K • G140A/C/S [34, 41] • Y143A/C/G/H/R/S [14] • N144D [42] • P145S [9] • S147G [19] • Q148E/G/H/K/R [6] • V151L [9] • N155H/S/T [6, 9] • E157Q [11, 35] • S230R [18, 31, 32, 33] • R263K [18] • L74F/I + V75I [36] 	

<p>DTG* 50 mg BID</p> <p>50 mg QD</p>	<ul style="list-style-type: none"> • G118R [12,13] • F121Y [17] • N144D [42] • V151L [9,23] • S153F/Y [9, 23, 26, 34] • R263K [16] • T66K + L74M [9] • E92Q + N155H [9, 21, 22] • Q148H/K/R + at least 2 mutations among: L74I or T97A or E138A/K/T or G140A/C/S [15, 38, 39] • Q148H/K/R + N155H [9, 27, 28] <ul style="list-style-type: none"> • G118R [12, 13] • F121Y [17] • E138A/K/T • G140A/C/S • N144D [42] • Q148H/K/R • V151L [9, 23] • S153F/Y [9, 23, 26, 34] • N155H [18] • S230R [29] • R263K [16] • T66K + L74M [9] • L74I + E92Q [30] 	<ul style="list-style-type: none"> • T66K [9] • Q148H/K/R + 1 mutation among: L74I or E138A/K/T or G140A/C/S [15] <ul style="list-style-type: none"> • T66K [9]
<p>CAB**</p>	<ul style="list-style-type: none"> • G118R [12, 13] • F121Y [17] • E138A/K/T • G140A/C/R/S [37] • N144D [42] • Q148H/K/R • V151L [9, 23] • S153F/Y [9, 23, 26, 34] • N155H [18] • S230R [29] 	<ul style="list-style-type: none"> • T66K [9]

	<ul style="list-style-type: none"> • R263K [16] • T66K + L74M [9] • L74I + E92Q [30] 	
<ul style="list-style-type: none"> • BIC** 	<ul style="list-style-type: none"> • G118R [12, 13] • F121Y [17] • E138A/K/T • G140A/C/S • N144D [42] • Q148H/K/R • V151L [9, 23] • S153F/Y [9, 23, 26, 34] • N155H [18] • S230R [29] • R263K [16] • T66K + L74M [9] • L74I + E92Q [30] 	<ul style="list-style-type: none"> • T66K [9]

RAL: raltegravir, EVG: elvitegravir, DTG: dolutegravir, CAB: cabotegravir, BIC: bictegravir

* Please note that rules are different for DTG 50 mg BID and 50 mg QD

**Due to few data and to the very close structures of dolutegravir, cabotegravir and bictegravir some rules for dolutegravir QD are transposed to cabotegravir and bictegravir

For DNA provirus, Impact of stop codons and G to A mutations on ARV resistance is unknown

REFERENCES

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

- 1/ Riva C et al. Transmitted virus with substitutions at position 215 and risk of virological failure in antiretroviral naive patients starting highly active antiretroviral therapy. XI International HIV drug resistance workshop: basic principles and clinical implications , 2-5 July 2002, Seville, Spain, abstract 124.
- 2/ Lanier ER et al. Effect of baseline 215D/C/S « revertant » mutations on virological response to lamivudine /zidovudine- containing regimens and emergence of 215Y upon virological failure. XI International HIV drug resistance workshop: basic principles and clinical implications, 2-5 July 2002, Seville, Spain abstract 146.
- 3/ Garcia-Lerma et al. Increased ability for selection of zidovudine resistance in a distinct class of wild-type HIV-1 from drug-naive persons. PNAS 2001 ; 98 : 13907-13912.
- 4/ Chappey C et al. Evolution of amino acid 215 in HIV-1 reverse transcriptase in response to intermittent drug selection. XII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2003, Los Cabos, Mexico, abstract 32.
- 5/ Brun-Vézinet F et al. Clinically relevant interpretation of genotype for resistance to abacavir: a study from the Narval trial (ANRS 088). AIDS 2003; 17(12):1795-802.
- 6/ Stone C, Ait-Khaled M, Craig C, Griffin P, Tisdale M. Human immunodeficiency virus type 1 reverse transcriptase mutation selection during in vitro exposure to tenofovir alone or combined with abacavir or lamivudine. Antimicrob Agents Chemother. 2004 Apr;48(4):1413-5.
- 7/ Miller MD et al. Multivariate analyses of antiviral response to tenofovir DF therapy in antiretroviral-experienced patients. XI International HIV drug resistance workshop: basic principles and clinical implications, 2-5 July 2002, Seville, Spain abstract 14.
- 8/ Margot NA, Lu B, Cheng A, Miller MD; Study 903 Team. Resistance development over 144 weeks in treatment-naive patients receiving tenofovir disoproxil fumarate or stavudine with lamivudine and efavirenz in Study 903. HIV Med. 2006 Oct;7(7):442-50.
- 9/ Parikh et al. K65R: a multi-nucleoside resistance mutation of a low but increasing frequency. XII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2003, Los Cabos, Mexico, abstract 136.
- 10/ Masquelier B et al. Genotypic and pharmacological determinants of the virological response to tenofovir in nucleoside reverse transcriptase inhibitor-experienced patients. Antivir Ther. 2004 ; 9(3):315-23.
- 11/ Mulamba GB et al. Pre-steady state kinetic analysis of the incorporation of FTC 5'-monophosphate and 3TC 5'-monophosphate by mutants HIV-1 RTs K65R, K65R/Q151M and Q151M. 16th International Conference on Antiviral Research, 27 April-1 May 2003, Savannah, USA. Abstract 39.

December 2020 - Version n°31

- 12/ Waters J et al. K65R, L74V and TAMs in HIV-1 RT associated with reduced response to tenofovir DF in antiretroviral-experienced patients. 13th Conference on Retroviruses and opportunistic Infections. 5-8 february 2006, Denver, Colorado, poster 633.
- 13/ Kagan RM, Lee TS, Ross L, Lloyd RM Jr, Lewinski MA, Potts SJ. Molecular basis of antagonism between K70E and K65R tenofovir-associated mutations in HIV-1 reverse transcriptase. *Antiviral Res.* 2007 Sep;75(3):210-8.
- 14/ Kagan R et al. Adefovir HIV-1 RT mutation K70E in the age of tenofovir. XIV International HIV Drug Resistance Workshop: basic principles and clinical implications, 7-11 June 2005, Québec City, Québec, Canada, abstract 93.
- 15/ Sluis-Cremer N, Sheen CW, Zelina S, Torres PS, Parikh UM, Mellors JW. Molecular mechanism by which the K70E mutation in human immunodeficiency virus type 1 reverse transcriptase confers resistance to nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother.* 2007 Jan;51(1):48-53.
- 16/ Miller V et al. HIV-1 reverse transcriptase (RT) genotype and susceptibility to RT inhibitors during abacavir monotherapy and combination therapy. *AIDS* 2000; 14:163–171.
- 17/ Moyle GJ, et al. Ziagen Once-Daily in Antiretroviral Combination Therapy (CNA30021) Study Team. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naïve HIV-infected adults: results of the Ziagen Once Daily in Antiretroviral Combination Study. *J Acquir Immune Defic Syndr.* 2005 Apr 1;38(4):417-25.
- 18/ Irlbeck D et al. Treatment-emergent mutations for previously naïve HIV-infected adults failing ZDV+3TC+EFV and ABC+3TC+EFV (CNA30024). 11th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, USA. February 8–11, 2004. Abstract 661.
- 19/ Gathe JC Jr et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS.* 2004 Jul 23;18(11):1529-37
- 20/ Wirden et al. Risk factors for selection of the L74I reverse transcriptase mutation in human immunodeficiency virus type 1-infected patients. *Antimicrob Agents Chemother.* 2006 Jul;50(7):2553-6.
- 21/ Wirden M et al., Antiretroviral combinations implicated in emergence of the L74I and L74V resistance mutations in HIV-1-infected patients. *AIDS.* 2009 Jan 2;23(1):95-9.
- 22/ Fourati S et al. Identification of a rare mutation at reverse transcriptase Lys65 (K65E) in HIV-1-infected patients failing on nucleos(t)ide reverse transcriptase inhibitors. *J Antimicrob Chemother.* 2013 Jun 19.
- 23/ Ross LL et al. A rare HIV reverse transcriptase mutation, K65N, confers reduced susceptibility to tenofovir, lamivudine and didanosine. *AIDS* 2006 Mar 21;20(5):787-9.
- 24/ Tisdale M et al. Combination of mutations in human immunodeficiency virus type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. *Antimicrob Agents Chemother.* 1997 May;41(5):1094-8.

25/Callebaut C et al. In Vitro Virology Profile of Tenofovir Alafenamide, a Novel Oral Prodrug of Tenofovir with Improved Antiviral Activity Compared to That of Tenofovir Disoproxil Fumarate. *Antimicrob Agents Chemother.* 2015 Oct;59(10):5909-16.

26/Margot NA et al. Rare emergence of drug resistance in HIV-1 treatment-naïve patients after 48 weeks of treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. *HIV Clin Trials.* 2016 Mar;17(2):78-87.

27/ Kawamoto et al. 2008. 2'-Deoxy-4'-C-ethynyl-2-halo-adenosines active against drug-resistant human immunodeficiency virus type 1 variants. *Int J Biochem Cell Biol.* 40, 2410–2420.

28/ Takamatsu et al. 2018 The high genetic barrier of EFdA/MK-8591 stems from strong interactions with the active site of drug-resistant HIV-1 reverse transcriptase. *Cell Chem Biol.* 2018; 25(10): 1268–1278.e3. doi:10.1016/j.chembiol.2018.07.014.

29/ Diamond T et al. Islatravir selects for HIV 1 variants in MT4 GFP cells that profoundly reduce replicative capacity in peripheral blood mononuclear cells. *HIV Glasgow 2020.* P120

Non nucleoside transcriptase inhibitors

1/ Harrigan PR, Mo T, Wynhoven B, Hirsch J, Brumme Z, McKenna P, Pattery T, Vingerhoets J, Bachelier LT. Rare mutations at codon 103 of HIV-1 reverse transcriptase can confer resistance to non-nucleoside reverse transcriptase inhibitors. *AIDS.* 2005 Mar 24;19(6):549-54.

2/ Brenner B et al. A V106M mutation in HIV-1 clade C viruses exposed to efavirenz confers cross-resistance to non-nucleoside reverse transcriptase inhibitors. *AIDS.* 2003 Jan 3;17(1):F1-5.

3/ Deshpande A et al. Resistance mutations in subtype C HIV type 1 isolates from Indian patients of Mumbai receiving NRTIs plus NNRTIs and experiencing a treatment failure: resistance to AR. *AIDS Res Hum Retroviruses* 2007; 23 : 335-40.

4/ Vingerhoets J et al. Impact of baseline NNRTI mutations on the virological response to TMC125 in the Phase III clinical trials DUET-1 and DUET-2. XVI International HIV drug resistance workshop : basic principles and clinical implications, 12-16 June 2007, Barbados, West Indies, abstract 32.

5/ Marcelin AG et al. Factors associated with virological response to etravirine in nonnucleoside reverse transcriptase inhibitor-experienced HIV-1-infected patients. *Antimicrob Agents Chemother.* 2010 Jan;54(1):72-7.

6/ Vingerhoets J et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled Phase III clinical studies. *AIDS.* 2010 Feb 20;24(4):503-14.

7/ Vingerhoets J et al. Impact of transmitted drug resistance (TDR) on virological response to initial combination antiretroviral therapy (cART). *Antiviral Therapy* 2010; 15 Suppl 2: A125 (abstract 99).

December 2020 - Version n°31

- 8/ El A et al. In vitro selection of novel etravirine-associated resistance mutations in B and non-B HIV-1 subtypes. *Antiviral Therapy* 2010; 15 Suppl 2: A134 (abstract 108).
- 9/ Azijn H et al. TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTI-resistant HIV-1. *Antimicrob Agents Chemother.* 2010 Feb;54(2):718-27.
- 10/Marcelin AG et al. Mutations selected in patients displaying treatment failure under an etravirine-containing regimen. *Antiviral Therapy* 2011; 10.3851/IMP1886.
- 11/ Maïga AI et al. Resistance-associated mutations to etravirine (TMC-125) in antiretroviral-naïve patients infected with non-B HIV-1 subtypes. *Antimicrob Agents Chemother.* 2010 Feb;54(2):728-33.
- 12/ Asahchop EL et al. Characterization of the E138K resistance mutation in HIV-1 reverse transcriptase conferring susceptibility to etravirine in B and non-B HIV-1 subtypes. *Antimicrob Agents Chemother.* 2011 Feb;55(2):600-7.
- 13/ Eron J et al. Characterization of the resistance profile of TMC278: 48-week analysis of the Phase III studies ECHO and THRIVE. 50th ICAAC 2010 (abstract H-1810).
- 14/ Haddad M et al. Impact of HIV-1 reverse transcriptase E138 mutations selected on rilpivirine drug susceptibility. *Antiviral Therapy* 2011; 16 Suppl 1: A18 (abstract 10).
- 15/ Haddad M et al. Combinations of HIV-1 reverse transcriptase mutations L100I+K103N/S and L100I+K103R+V179D reduce susceptibility to rilpivirine. 53rd ICAAC 2013 (abstract H-677)
- 16/ Melikian et al. Non-nucleoside reverse transcriptase inhibitor (NNRTI) cross-resistance: implications for preclinical evaluation of novel NNRTIs and clinical genotypic resistance testing. *J Antimicrob Chemother.* 2014 Jan;69(1):12-20.
- 17/ Lai MT et al. In vitro characterization of MK-1439, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor. *Antimicrob Agents Chemother.* 2014;58(3):1652-63.
- 18/ Feng M, et al. In vitro resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways. *Antimicrob Agents Chemother.* 2015 Jan;59(1):590-8.
- 19/ Feng M, et al. Doravirine Suppresses Common Nonnucleoside Reverse Transcriptase Inhibitor-Associated Mutants at Clinically Relevant Concentrations. *Antimicrob Agents Chemother.* 2016 Mar 25;60(4):2241-7.
- 20/ Smith SJ, et al. Rilpivirine and Doravirine Have Complementary Efficacies Against NNRTI-Resistant HIV-1 Mutants. *J Acquir Immune Defic Syndr.* 2016 Aug 15;72(5):485-91.

21/ Lai MT et al. Characterization of Doravirine-Selected Resistance Patterns from Participants in Treatment-Naïve Phase 3 Clinical Trials. Abstract THPDB0101. 22nd International AIDS Conference, Amsterdam, the Netherlands, 23-27 July 2018.

22/ Raymond S et al. Impact of Human Immunodeficiency Virus Type 1 Minority Variants on the Virus Response to a Rilpivirine-Based First-line Regimen. Clin Infect Dis. 2018 May 2;66(10):1588-1594.

23/ Saladini F et al. In vitro analysis of doravirine activity on HIV-1 clones harboring multiple NNRTI resistance mutations. Abstract PS5/6, EACS 2019, Basel, Switzerland, Nov 6-9, 2019

Protease inhibitors

1/ Marcelin AG, Cohen-Codar I, King MS, Colson P, Guillevic E, Descamps D, Lamotte C, Schneider V, Ritter J, Segondy M, Peigue-Lafeuille H, Morand-Joubert L, Schmuck A, Ruffault A, Palmer P, Chaix ML, Mackiewicz V, Brodard V, Izopet J, Cottalorda J, Kohli E, Chauvin JP, Kempf DJ, Peytavin G, Calvez V. Virological and pharmacological parameters predicting the response to lopinavir-ritonavir in heavily protease inhibitor-experienced patients. Antimicrob Agents Chemother. 2005 May;49(5):1720-6.

2/ Maillard A, Chaplain JM, Tribut O, Bentué-Ferrer D, Tattevin P, Arvieux C, Michelet C, Ruffault A. The use of drug resistance algorithms and genotypic inhibitory quotient in prediction of lopinavir-ritonavir treatment response in human immunodeficiency virus type 1 protease inhibitor-experienced patients. J Clin Virol. 2007 Feb;38(2):131-8.

3/ Masquelier B et al. Human Immunodeficiency virus type 1 genotypic and pharmacokinetic determinants of the virological response to lopinavir-ritonavir-containing therapy in protease inhibitor-experienced patients. Antimicrob Agents and Chemother 2002 ; 46 : 2926-2932.

4/ Colonna RJ et al. Identification of I50L as the signature atazanavir (ATV)-resistance mutation in treatment naïve HIV-1 infected patients receiving ATV-containing regimens. Journal of Infectious Diseases 2004; 189: 1802-10.

5/ Vora S et al. Clinical validation of atazanavir/ritonavir genotypic resistance score in PI-experienced patients. AIDS 2006 Jan 2;20(1):35-40.

6/ Marcelin AG et al. Tipranavir-ritonavir genotypic resistance score in protease inhibitor-experienced patients. Antimicrob Agents Chemother. 2008 Sept;52(9).

7/ Marcelin AG et al. External validation of atazanavir/ritonavir genotypic score in HIV-1 protease inhibitor experienced patients. JAIDS 2006; 42 (1): 127-8.

8/ Friend J et al. Isolated lopinavir resistance after virological rebound of a ritonavir/lopinavir-based regimen. AIDS. 2004 Sep 24;18(14):1965-6.

9/ de Mendoza C et al. Prevalence of the HIV-1 protease mutation I47A in clinical practice and association with lopinavir resistance. AIDS 2006 Apr 24; 20(7): 1071-4.

December 2020 - Version n°31

10/ de Meyer S, Vangeneugden T, van Baelen B, de Paepe E, van Marck H, Picchio G, Lefebvre E, de Béthune MP. Resistance profile of darunavir: combined 24-week results from the POWER trials. *AIDS Res Hum Retroviruses*. 2008 Mar;24(3):379-88.

11/ Nijhuis N et al. A novel genetic pathway involving L76V and M46I leading to lopinavir/r resistance. XVI International HIV drug resistance workshop : basic principles and clinical implications, 12-16 June 2007, Barbados, West Indies, abstract 127.

12/ Delaugerre C et al. Protease inhibitor resistance analysis in the MONARK trial comparing first-line lopinavir-ritonavir monotherapy to lopinavir-ritonavir plus zidovudine and lamivudine triple therapy. *Antimicrob Agents Chemother*. 2009 Jul;53(7):2934-9.

13/ Hill A et al. Identification of new genotypic cut-off levels to predict the efficacy of lopinavir/ritonavir and darunavir/ritonavir in the TITAN trial. *HIV Med*. 2009 Jul 6.

14/ Di Giambenedetto S et al. A rigorous statistical learning method for the estimation and validation of weighted drug susceptibility scores applied to in vivo virological outcome prediction in atazanavir/ritonavir-containing HAART. XVII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2008, Sitges, Spain, abstract 95.

15/ Bethell R et al. No effect of subtype on susceptibility and virological response to TPV/r for treatment experienced patients. XVII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2008, Sitges, Spain, abstract 111.

16/ Descamps D et al. Mutations associated with virological response to darunavir/ritonavir in HIV-1-infected protease inhibitor-experienced patients. *J Antimicrob Chemother*. 2009 Mar;63(3):585-92.

17/ De Meyer S. et al. Influence of baseline protease inhibitor resistance on the efficacy of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial. *J Acquir Immune Defic Syndr*. 2008 Dec 15;49(5):563-4.

18/ De Meyer S. et al. Phenotypic and genotypic determinants of resistance to darunavir: analysis of data from treatment-experienced patients in POWER 1, 2, 3 and DUET-1 and 2. XVII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2008, Sitges, Spain, abstract 31.

19/ De Meyer S. et al. Confirmation of the negative impact of protease mutations I47V, I54M, T74P and I84V and the positive impact of protease mutation V82A on virological response to darunavir/ritonavir. XVII International HIV drug resistance workshop: basic principles and clinical implications, 9-13 June 2009, Fort Myers, Florida, abstract 126.

20/ Gong YF. et al. In vitro resistance profile of the human immunodeficiency virus type 1 protease inhibitor BMS-232632. *Antimicrob Agents Chemother*. 2000 Sep;44(9):2319-26.

21/ Malan DR; et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naïve patients. *J Acquir Immune Defic Syndr*. 2008 Feb 1;47(2):161-7.

December 2020 - Version n°31

22/ Malan DR et al. 96-week efficacy and safety of atazanavir, with and without ritonavir, in a HAART regimen in treatment-naive patients. *J Int Assoc Physicians AIDS Care (Chic)*. 2010 Jan-Feb;9(1):34-42.

23/ Lambert-Niclot et al. Emerging resistance mutations in protease inhibitor naive patients failing atazanavir based regimen (ANRS multicenter observational study). *Journal of Antimicrobial Chemotherapy* 21-Mar-2018 (in press)

Fusion inhibitor

1/ Sista P et al. Subgroup analysis of baseline susceptibility and early virological response to enfuvirtide in the combined TORO studies. XII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2003, Los Cabos, Mexico, abstract 55.

2/ Mink M et al. Impact of HIV-1 gp41 amino acid substitutions (position 36-45) on susceptibility to T20 (enfuvirtide) in vitro; analysis of primary virus isolates recovered from patients during chronic enfuvirtide treatment and site-directed mutants in NL4-3. XI International HIV drug resistance workshop: basic principles and clinical implications, 2-5 July 2002, Seville, Spain, abstract 22.

3/ Greenberg ML et al. Enfuvirtide (T-20) and T-1249 resistance: observations from phase II clinical trials of enfuvirtide in combination with oral antiretrovirals and a phase I/II dose-ranging monotherapy trial of T-1249. XI International HIV drug resistance workshop: basic principles and clinical implications, 2-5 July 2002, Seville, Spain, abstract 128.

4/ Greenberg ML et al. Baseline and on-treatment susceptibility to enfuvirtide seen in TORO 1 and TORO 2 to 24 weeks. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, USA, abstract 141.

5/ Chakraborty B et al. Replicative fitness of HIV-1 strains with reduced susceptibility to protease-, reverse transcriptase- and entry (enfuvirtide)-inhibitors. XIII International HIV drug resistance workshop: basic principles and clinical implications, 8-12 June 2004, Tenerife, Spain, abstract 61.

6/ Walmsley SL et al. Development of a new genotypic resistance assay involving the entire gp41 sequence for evaluating resistance to enfuvirtide. XIII International HIV drug resistance workshop: basic principles and clinical implications, 8-12 June 2004, Tenerife, Spain, abstract 134.

7/ Melby T et al. Evolution of enfuvirtide resistance in longitudinal samples obtained after continued enfuvirtide dosing post-virological failure. XIV International HIV Drug Resistance Workshop: basic principles and clinical implications, 7-11 June 2005, Québec City, Québec, Canada, abstract 67.

Attachment Inhibitor

December 2020 - Version n°31

1/Zhou N et al. Genotypic correlates of susceptibility to HIV-1 attachment inhibitor BMS-626529, the active agent of the prodrug BMS-663068. *J Antimicrob Chemother* 2014; 69: 573–81.

2/Ray N et al. Prediction of virological response and assessment of resistance emergence to the HIV-1 attachment inhibitor BMS-626529 during 8-day monotherapy with its prodrug BMS-663068. *J Acquir Immune Defic Syndr* 2013; 64: 7–15.

3/Lataillade M et al. Viral drug resistance through 48 weeks, in a phase 2b, randomized, controlled trial of the HIV-1 attachment inhibitor prodrug, Fostemsavir. *J Acquir Immune Defic Syndr*. 2018 Mar 1;77(3):299-307.

4/ Alessandri-Gradt E et al. Impact of natural polymorphisms of HIV-1 non-group M on genotypic susceptibility to the attachment inhibitor fostemsavir. *J Antimicrob Chemother* 2018; 73: 2716–2720.

5/ Lataillade et al. Fostemsavir (FTR) Week 48 efficacy and evaluation of treatment-emergent substitutions in the BRIGHT study. 17th European meeting on HIV and Hepatitis. May 22-24, 2019. Rome, Italy, Abstract n°8.

Integrase strand transfer inhibitor

1/ Cooper DA et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med*. 2008 Jul 24;359(4):355-65.

2/ Malet I et al. Mutations associated with failure of raltegravir treatment affect integrase sensitivity to the inhibitor in vitro. *Antimicrob Agents Chemother*. 2008 Apr;52(4):1351-8.

3/ Hatano H et al. Evolution of integrase resistance during failure of integrase inhibitor-based antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2010 Aug 1;54(4):389-93.

4/ Da Silva D et al. HIV-1 resistance patterns to integrase inhibitors in antiretroviral-experienced patients with virological failure on raltegravir-containing regimens. *J Antimicrob Chemother*. 2010 Jun;65(6):1262-9

5/ Ceccherini-Silberstein F et al. Virological response and resistance in multi-experienced patients treated by raltegravir. XVII International HIV drug resistance workshop: basic principles and clinical implications, 10-14 June 2008, Sitges, Spain, abstract 18.

6/ Waters J et al. Evolution of resistance to the HIV integrase inhibitor (INI) elvitegravir can involve genotypic switching among primary INI resistance patterns. XVII International HIV drug resistance workshop: basic principles and clinical implications, 9-13 June 2009, Fort Myers, Florida, abstract 116.

7/ Geretti AM et al. Prevalence and patterns of raltegravir resistance in treated patients in Europe. *Antiviral Therapy* 2010; 15 Suppl 2: A62 (abstract 51)

8/ Huang W et al. Identification of alternative amino acid substitutions at HIV-1 integrase codon 143 that confer reduced susceptibility to raltegravir. 18th Conference on Retroviruses and Opportunistic Infections, February 27-March 2, 2011, Boston, USA, abstract 607.

December 2020 - Version n°31

- 9/ Kobayashi M et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. *Antimicrob Agents Chemother.* 2011 Feb;55(2):813-21.
- 10/ Malet I et al. The HIV-1 integrase G118R mutation confers raltegravir resistance to the CRF02_AG HIV-1 subtype. *J Antimicrob Chemother.* 2011 Dec;66(12):2827-30.
- 11/ White K et al. Integrated Analysis of Emergent Drug Resistance from the HIV-1 Phase 3 QUAD Studies through Week 48. International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies June 5-9, 2012 Sitges, Spain, Abstract 4.
- 12/ Bar-Magen et al. Identification of novel mutations responsible for resistance to MK-2048, a second-generation HIV-1 integrase inhibitor. *J Virol.* 2010 Sep;84(18):9210-6.
- 13/ Hare S et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). *Mol Pharmacol.* 2011 Oct;80(4):565-72.
- 14/ Huang W et al. Contribution of raltegravir selected secondary mutations to reduction in elvitegravir susceptibility of patient-derived HIV integrase containing Y143 mutations. International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies June 4-8, 2013 Toronto, Canada, Abstract 89.
- 15/ Vavro CL et al. Integrase genotypic and phenotypic predictors of antiviral response to dolutegravir (DTG) in subjects with resistance to integrase inhibitors (INIs). International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies June 4-8, 2013 Toronto, Canada, Abstract 29.
- 16/ Underwood MR et al. Analysis and characterization of treatment-emergent resistance in ART-experienced, integrase inhibitor-naïve subjects with dolutegravir (DTG) versus raltegravir (RAL) in SAILING (ING111762). International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies June 4-8, 2013 Toronto, Canada, Abstract 21.
- 17/ Malet I et al. New raltegravir resistance pathways induce broad cross-resistance to all currently used integrase inhibitors. *J Antimicrob Chemother.* 2014 Aug;69(8):2118-22.
- 18/ Underwood MR et al. Resistance Post Week 48 in ART-Experienced, Integrase Inhibitor-Naïve Subjects with Dolutegravir (DTG) vs. Raltegravir (RAL) in SAILING (ING111762). 13th European HIV & Hepatitis workshop, June 3-5 2015, Barcelona, Spain (Abstract n°6)
- 19/ Molina et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis.* 2012 Jan;12(1):27-35.
- 20/ Sax et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet.* 2012 Jun 30;379(9835):2439-48.
- 21/ Underwood et al. The activity of the integrase inhibitor dolutegravir against HIV-1 variants isolated from raltegravir-treated adults. *J Acquir Immune Defic Syndr.* 2012 Nov 1;61(3):297-301.

- 22/ Frantzell et al. Dolutegravir resistance requires multiple primary mutation in HIV-1 integrase. CROI 2015. Abstract Number: 121.
- 23/ Yoshinoga et al. Antiviral characteristics of GSK1265744, an HIV integrase inhibitor dosed orally or by long-acting injection. *Antimicrob Agents Chemother.* 2015 Jan;59(1):397-406
- 24/ Margolis et al. 744 and Rilpivirine As Two Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results. CROI 2014. Abstract Number: 91LB
- 25/ Dudas et al. Characterization of NNRTI and INI Resistance Mutations Observed in a Study Subject on Oral Two-Drug Maintenance Therapy with 10 mg Cabotegravir + 25 mg Rilpivirine. IHDRW 2015 Seattle, WA, USA. Abstract 13.
- 26/ Abram ME, Ram RR, White KL, Miller MD, Callebaut C. Pre-existing HIV-1 integrase polymorphisms do not impact treatment response to elvitegravir-containing fixed-dose combination regimens in treatment-naive patients. HIV Drug Therapy 2016 Glasgow. The poster can be found at:
http://s3-eu-west-1.amazonaws.com/hivglasgow/wp-content/uploads/2016/12/07153921/3.-Treatment-Strategies-Target-Populations_Poster-Book.pdf
- 27/ Huang W et al. Impact of Raltegravir/Elvitegravir Selected Mutations on Dolutegravir Cross-resistance. CROI March 3-6, 2014, Boston, MA, USA. Abstract 595.
- 28/ Blanco JL et al. Pathways of resistance in subjects failing dolutegravir monotherapy. CROI February 13–16, 2017, Seattle, WA, USA. Abstract 42
- 29/ Wijting I et al. Dolutegravir as maintenance monotherapy for HIV-1: a randomized clinical trial. CROI February 13–16, 2017, Seattle, WA, USA. Abstract LB451
- 30/ Katlama C et al. Dolutegravir as monotherapy in HIV-1-infected individuals with suppressed HIV viraemia. *J Antimicrob Chemother.* 2016 Sep;71(9):2646-50
- 31/ Goethals O et al. Resistance mutations in human immunodeficiency virus type 1 integrase selected with elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors. *J Virol.* 2008 Nov;82(21):10366-74.
- 32/ Blanco JL et al. HIV-1 integrase inhibitor resistance and its clinical implications. *J Infect Dis.* 2011 May 1;203(9):1204-14.
- 33/ Pham HT et al. Characterization of the dolutegravir monotherapy-acquired S230R resistance mutation. CROI March 4-7, 2018, Boston, MA, USA. Abstract 548.
- 34/ Andreatta K et al. Integrase inhibitor resistance selections initiated with drug resistant HIV-1. CROI March 4-7, 2018, Boston, MA, USA. Abstract 546.
- 35/ Charpentier C et al. Phenotypic analysis of HIV-1 E157Q integrase polymorphism and impact on virological outcome in patients initiating an integrase inhibitor-based regimen. *J Antimicrob Chemother.* 2018 Apr 1;73(4):1039-1044.
- 36/ Hachiya A et al. Impact of clinically observed integrase mutations on dolutegravir. CROI February 13–16, 2017, Seattle, WA, USA. Abstract 496.
- 37/ Orkin C et al. Long-acting CABOTEGRAVIR + RILPIVIRINE for HIV maintenance: FLAIR Week 48 results. CROI 2019, Seattle, WA, USA. Abs. 140LB.

December 2020 - Version n°31

38/ George JM et al. Rapid Development of High-Level Resistance to Dolutegravir With Emergence of T97A Mutation in 2 Treatment-Experienced Individuals With Baseline Partial Sensitivity to Dolutegravir. *Open Forum Infect Dis.* 2018 Sep 8;5(10):221.

39/ White K et al. Potent activity of GS-9883, a novel unboosted HIV-1 integrase strand transfer inhibitor (INSTI), against patients isolates with ISNTI-resistance. 14th European HIV & Hepatitis workshop, May 2016, Roma, Italy (Abstract 0_1).

40/ Margot NA et al. In vitro resistance selections using elvitegravir, raltegravir, and two metabolites of elvitegravir M1 and M4. *Antiviral Res.* 2012 Feb;93(2):288-296.

41/ Goethals O et al. Primary mutations selected in vitro with raltegravir confer large fold changes in susceptibility to first-generation integrase inhibitors, but minor fold changes to inhibitors with second-generation resistance profiles. *Virology.* 2010 Jul 5;402(2):338-46.

42/ Andreatta K et al. Long-term Bictegravir and Dolutegravir Resistance Selections Initiated with HIV-1 Containing M184V in Reverse Transcriptase. Abstract 9. European Meeting on HIV & Hepatitis 2020.