

ANRS - AC 11 : 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"> • T215Y/F <ul style="list-style-type: none"> • At least 3 mutations among : M41L, D67N, K70R, L210W, T215A/C/D/E/G/H/I/L/N/S/V, K219Q/E [1, 2, 3, 4] • Q151M • Insertion at codon 69 	<ul style="list-style-type: none"> • T215A/C/D/E/G/H/I/L/N/S/V [1, 2, 3, 4]
3TC/FTC	<ul style="list-style-type: none"> • M184V/I • Insertion at codon 69 	<ul style="list-style-type: none"> • K65R [11, 12, 16] • Q151M
ddl	<ul style="list-style-type: none"> • At least a score of + 2 among: M41L + T69D + L74V/I + 215Y/F + K219Q/E – K70R – M184 V/I [5, 14, 15, 17, 18] • L74V/I without any mutations among M41L, T69D, K70R, M184 V/I, T215Y/F, K219Q/E [19] • Q151M • Insertion at codon 69 	<ul style="list-style-type: none"> • K65R [11, 12]
d4T	<ul style="list-style-type: none"> • V75A/M/S/T • T215Y/F [6] <ul style="list-style-type: none"> • At least 3 mutations among : M41L, D67N, K70R, L210W, T215A/C/D/E/G/H/I/L/N/S/V, K219Q/E [4, 7, 14, 15] • K65R [30, 31, 32] • Q151M • Insertion at codon 69 	<ul style="list-style-type: none"> • T215A/C/D/E/G/H/I/L/N/S/V [4, 7]
ABC	<ul style="list-style-type: none"> • At least 5 mutations among : M41L, D67N, L74V/I, M184V/I, L210W, T215Y/F [8, 19, 29] • No TAMs and at least 2 mutations among: K65R, L74V/I, Y115F and M184V/I [24, 25, 26, 27, 28, 29] • Q151M • Insertion at codon 69 	<ul style="list-style-type: none"> • 4 mutations among : M41L, D67N, L74V/I, M184V/I, L210W, T215Y/F [8, 19, 29] • K65R [9, 11, 12] • Y115F
TDF	<ul style="list-style-type: none"> • At least 6 mutations among: M41L, E44D, D67N, T69D/N/S, L74V/I, L210W, T215Y/F [13, 20,33] • K65R [9, 10, 11, 12] • Insertion at codon 69 	<ul style="list-style-type: none"> • 3, 4 or 5 mutations among: M41L, E44D, D67N, T69D/N/S, L74V/I, L210W, T215Y/F [13,33] • K70E [21, 22, 23]

July 2010- Version n°19

TAMs = M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

ZDV: zidovudine, 3TC: lamivudine, FTC: emtricitabine, ddl: didanosine, d4T: stavudine, ABC: abacavir, TDF: tenofovir

Mutations associated with antiretroviral regimen but with uncertain signification: E44A, D67E/G, T69A, K219N/R

**ANRS - AC 11 : 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] • 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 	
ETR	<ul style="list-style-type: none"> • At least 4 among: V90I, A98G, L100I, K101E/H/I/P/R, V106I, V179D/F/I/L/M/T, Y181C/I, G190A/S, M230L [4,7,8,9, 10, 11] • Y181V [5, 6] • Y181C+H221Y [7] 	<ul style="list-style-type: none"> • 3 mutations among: V90I, A98G, L100I, K101E/H/I/P/R, V106I, V179D/F/I/L/M/T, Y181C/I, G190A/S, M230L [4,7,8,9, 10, 11] • E138A/G/K/Q/R [5, 6, 7, 8]

EFV: efavirenz, NVP: nevirapine, ETR: etravirine

Mutations associated with antiretroviral regimen but with uncertain signification: K101H/N/Q

**ANRS - AC 11 : RESISTANCE GROUP
GENOTYPE INTERPRETATION: PROTEASE INHIBITORS**

	Mutations associated with resistance	Mutations associated with « possible resistance »
IDV	<ul style="list-style-type: none"> • M46I/L • V82A/F/M/S/T [11] • I84A/V [8] • L90M and at least 2 among : K20M/R, L24I, V32I, M36I, I54V/L/M/T, A71V/T, G73S/A, V77I 	<ul style="list-style-type: none"> • L90M
SQV/RTV 1000/100 mg BID	<ul style="list-style-type: none"> • G48V • At least 4 mutations among: L10F/I/M/R/V, I15A/V, K20I/M/R/T, L24I, I62V, G73S/T, V82A/F/S/T, I84V, L90M [9] 	<ul style="list-style-type: none"> • 3 mutations among: L10F/I/M/R/V, I15A/V, K20I/M/R/T, L24I, I62V, G73S/T, V82A/F/S/T, I84V, L90M [9]
NFV	<ul style="list-style-type: none"> • D30N • I84A/V [8] • N88S/D • L90M 	<ul style="list-style-type: none"> • V82A/F/S/T and at least 2 among: L10I, M36I, M46I/L, I54V/L/M/T, A71V/T, V77I [1]
FPV/RTV 700/100 mg BID	<ul style="list-style-type: none"> • I50V • V32I and I47A/V [2, 13, 14] • At least 4 mutations among: L10F/I/V, L33F, M36I, I54A/L/M/S/T/V, I62V, V82A/C/F/G, I84V, L90M [2, 20] 	
LPV/r	<ul style="list-style-type: none"> • At least 6 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 [3, 4, 5, 21] • I47A [15, 16] • L76V [18, 19] 	<ul style="list-style-type: none"> • 4 or 5 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 [3, 4, 5, 21]
ATV/RTV 300/100 mg QD	<ul style="list-style-type: none"> • I50L [6] • At least 3 mutations among: L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, I84V, I85V, L90M [7, 12, 22] 	
TPV/RTV 500/200 mg BID	<ul style="list-style-type: none"> • At least a score of + 3* : 36I/L/V – 53L/W/Y + 58E + 69I/K/N/Q/R/Y + 89I/M/R/T/V [10, 23] 	<ul style="list-style-type: none"> • A score of + 2* : 36I/L/V – 53L/W/Y + 58E + 69I/K/N/Q/R/Y + 89I/M/R/T/V [10, 23]
DRV/RTV 600/100 mg BID	<ul style="list-style-type: none"> • At least 4 mutations among: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V [17, 24, 25, 26] 	<ul style="list-style-type: none"> • 3 mutations among: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V [17, 24, 25, 26]

July 2010- Version n°19

**IDV: indinavir, SQV: saquinavir, NFV: nelfinavir, RTV: ritonavir, FPV: fosamprenavir, LPV: lopinavir, ATV:atazanavir, TPV: tipranavir,
DRV : darunavir**

Mutations associated with antiretroviral regimen but with uncertain signification: K20T, M46V

N88S mutation is associated with better virological response to fosamprenavir [2]

V82A is associated with better virological response to darunavir [27]

*** Insufficient data for HIV-1 subtype non-B**

ANRS - AC 11 : 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

ANRS - AC 11 : RESISTANCE GROUP

GENOTYPE INTERPRETATION: INTEGRASE INHIBITORS

	Mutations associated with resistance	Mutations associated with possible resistance
RAL	<ul style="list-style-type: none"> • Q148H/G/K/R/E [1, 2] • N155H [1, 2] • E157Q [2] • E92Q [1, 2] • G140A/S [7] • Y143C/H/R [1, 3, 4, 5] 	<ul style="list-style-type: none"> • 3 mutations among : V72I, L74M, T97A, V151I, G163R, S230R [8]
EVG	<ul style="list-style-type: none"> • T66I/A/K [6] • E92Q [6] • E138K • G140C/S • S147G • Q148H/R/K [6] • N155H [6] 	

RAL: raltegravir, EVG: elvitegravir

**ANRS - AC 11 : RESISTANCE GROUP
GENOTYPE INTERPRETATION FOR HIV-2**

NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS
<ul style="list-style-type: none">• K65R : Resistance to ddl, TDF, ABC [1]• Q151M : all NRTI except 3TC and FTC [1]• M184V : Resistance to 3TC/FTC [1]
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
<ul style="list-style-type: none">• Naturally resistant to all NNRTI [2, 3]
PROTEASE INHIBITORS
<ul style="list-style-type: none">• Naturally resistant to APV and fosAPV [2, 3] <p>Contradictory data for ATV , TPV [2, 4]</p>
FUSION INHIBITOR
<ul style="list-style-type: none">• Naturally resistant to T20 [2, 3]
INTEGRASE INHIBITORS
<ul style="list-style-type: none">• Y143C/H/R : resistance to raltegravir [7]• Q148K/R : Resistance to raltegravir [5]• N155H : Resistance to raltegravir [6]

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/ Costagliola D et al. Presence of thymidine –associated mutations and response to d4T, abacavir and ddi in the control arm of the Narval ANRS 088 trial. 8th Conference on Retroviruses and opportunistic Infections. 4-8 february 2001, Chicago, Illinois, poster 450.
- 6/ Calvez V et al. Impact of stavudine phenotype and thymidine analogs mutations on viral response to stavudine plus lamivudine in ALTIS 2 ANRS trial. Antiviral Therapy 2002, 7(3):211-218.
- 7/ García-Lerma JG, MacInnes H, Bennett D, Reid P, Nidtha S, Weinstock H, Kaplan JE, Heneine W. A novel genetic pathway of human immunodeficiency virus type 1 resistance to stavudine mediated by the K65R mutation. J Virol. 2003 May;77(10):5685-93.
- 8/ 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.
- 9/ 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.
- 10/ 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.
- 11/ 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.
- 12/ 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.

July 2010- Version n°19

- 13/ 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.
- 14/ Izopet J. et al. Mutations conferring resistance to zidovudine diminish the antiviral effect of stavudine plus didanosine. *Journal of Medical Virology* 1999 ; 59 : 507-511.
- 15/ Pellegrin I. et al. Emergence of zidovudine and multidrug-resistance mutations in the HIV-1 reverse transcriptase gene in therapy-naive patients receiving stavudine plus didanosine combination therapy. STADI group. *AIDS* 1999 ; 13 : 1705-1709.
- 16/ 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.
- 17/ Marcelin AG et al. Clinically relevant genotype interpretation of resistance to didanosine. *Antimicrob Agents Chemother.* 2005 May;49(5):1739-44.
- 18/ Capdepon S et al. An additive/subtractive genotypic score as a determinant of the virological response to didanosine in HIV-1 infected patients. *J Clin Virol.* 2006 May;36(1): 36-42.
- 19/ Assoumou L, Brun-Vézinet F, Cozzi-Lepri A, Kuritzkes D, Phillips A, Zolopa A, Degruittola V, Miller V, Costagliola D; Standardization and Clinical Relevance of HIV Drug Resistance Testing Project of the Forum for Collaborative HIV Research. Initiatives for Developing and Comparing Genotype Interpretation Systems: External Validation of Existing Systems for Didanosine against Virological Response. *J Infect Dis.* 2008 Jul 3.
- 20/ 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.
- 21/ 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.
- 22/ 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.
- 23/ 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.
- 24/ 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.
- 25/ 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-naive 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.

July 2010- Version n°19

26/ 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.

27/ Rodriguez-French A, *et al.* The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2004; **35**:22–32.

28/ Gathe JC Jr *et al.* SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naïve HIV-1-infected patients. *AIDS*. 2004 Jul 23;18(11):1529-37

29/ 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.

30/García-Lerma JG *et al.* A novel genetic pathway of human immunodeficiency virus type 1 resistance to stavudine mediated by the K65R mutation. *J Virol*. 2003 May;77(10):5685-93

31/Sungkanuparph S *et al.* Prevalence and risk factors for developing K65R mutations among HIV-1 infected patients who fail an initial regimen of fixed-dose combination of stavudine, lamivudine, and nevirapine. *J Clin Virol*. 2008 ;41:310-3.

32/Coutsinos D *et al.* The K65R mutation subtype B and C HIV-1: rates of development and the implications of template-specific dislocation mutagenesis. *Antiviral Therapy* 2010; 15 suppl 2:A13 (abs 5)

33/ 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.

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 *et al.* Factors associated with early virological response to etravirine in NNRTI experienced HIV-infected patients. 16th Conference on Retroviruses and Opportunistic Infections. 8-11 February 2009, Montreal, Canada, abstract 645.

July 2010- Version n°19

6/ Vingerhoets et al. An update of the list of NNRTI mutations associated with decreased virologic response to etravirine (ETR): multivariate analyses on the pooled DUET-1 and DUET-2 clinical trial data. XVII International HIV drug resistance workshop : basic principles and clinical implications, 10-14 June 2008, Sitges, Spain, abstract 24.

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).

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* 2010; 15 Suppl 2: A64 (abstract 53).

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.

Protease inhibitors

1/ Phenotype/genotype correlation from Stanford database.

2/ Masquelier B, Assoumou KL, Descamps D, Bocket L, Cottalorda J, Ruffault A, Marcelin AG, Morand-Joubert L, Tamalet C, Charpentier C, Peytavin G, Antoun Z, Brun-Vézinet F, Costagliola D; ANRS Resistance Study Group. Clinically validated mutation scores for HIV-1 resistance to fosamprenavir/ritonavir. *J Antimicrob Chemother.* 2008 Jun;61(6):1362-8.

3/ 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.

4/ 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.

5/ 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.

July 2010- Version n°19

- 6/ 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.
- 7/ Vora S et al. Clinical validation of atazanavir/ritonavir genotypic resistance score in PI-experienced patients. *AIDS* 2006 Jan 2;20(1):35-40.
- 8/ Mo H, Parkin N, Stewart KD, Lu L, Dekhtyar T, Kempf DJ, Molla A. Identification and structural characterization of I84C and I84A mutations that are associated with high-level resistance to human immunodeficiency virus protease inhibitors and impair viral replication. *Antimicrob Agents Chemother.* 2007 Feb;51(2):732-5.
- 9/ Marcelin AG, Flandre P, de Mendoza C, Roquebert B, Peytavin G, Valer L, Wirden M, Abbas S, Katlama C, Soriano V, Calvez V. Clinical validation of saquinavir/ritonavir genotypic resistance score in protease-inhibitor-experienced patients. *Antivir Ther.* 2007;12(2):247-52.
- 10/ Marcelin AG et al. Tipranavir-ritonavir genotypic resistance score in protease inhibitor-experienced patients. *Antimicrob Agents Chemother.* 2008 Sept;52(9).
- 11/ Camacho R et al. Different substitutions under selective pressure at protease codon 82 in HIV-1 subtype G compared to subtype B infected individuals including a novel I82M resistance mutation. XIV International HIV Drug Resistance Workshop: basic principles and clinical implications, 7-11 June 2005, Québec City, Québec, Canada, abstract 138.
- 12/ Marcelin AG et al. External validation of atazanavir/ritonavir genotypic score in HIV-1 protease inhibitor experienced patients. *JAIDS* 2006; 42 (1): 127-8.
- 13/ Brutus A et al. The Neat Study: Virologic response in subjects receiving GW433908 (908) BID by viral load/CD4 cell Counts at study entry. XV International AIDS Conference, July 11-16 2004, Bangkok ,Thailand, abstract TuPeB 4500.
- 14/ Pellegrin I, Breilh D, Coureau G, Boucher S, Neau D, Merel P, Lacoste D, Fleury H, Saux MC, Pellegrin JL, Lazaro E, Dabis F, Thiébaud R; ANRS Co3 Aquitaine Cohort. Interpretation of genotype and pharmacokinetics for resistance to fosamprenavir-ritonavir-based regimens in antiretroviral-experienced patients. *Antimicrob Agents Chemother.* 2007 Apr;51(4):1473-80.
- 15/ Friend J et al. Isolated lopinavir resistance after virological rebound of a ritonavir/lopinavir-based regimen. *AIDS.* 2004 Sep 24;18(14):1965-6.
- 16/ 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.
- 17/ 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.
- 18/ 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.
- 19/ 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.

July 2010- Version n°19

20/ Marcelin AG et al. Genotypic resistance analysis of the virological response to fosamprenavir-ritonavir in protease inhibitor-experienced patients in CONTEXT and TRIAD clinical trials. *Antimicrob Agents Chemother.* 2008 Dec;52(12):4251-7.

21/ 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.

22/ 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.

23/ 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.

24/ 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.

25/ 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.

26/ 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.

27/ 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.

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.

July 2010- Version n°19

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.

Integrase inhibitors

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. Virological and immunological outcomes in a cohort of patients failing integrase inhibitors. XVII International HIV drug resistance workshop : basic principles and clinical implications, 10-14 June 2008, Sitges, Spain, abstract 10.

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/ Fransen S et al. Comparison of Raltegravir Susceptible and Resistant Viruses Define the Contribution of Secondary Mutations to Reductions in Raltegravir Susceptibility. 17th Conference on Retroviruses and Opportunistic Infection, San Francisco, CA 16-19 February 2010 (abstract 556).

July 2010- Version n°19

HIV-2

- 1/ Damond F et al. In vitro phenotypic susceptibility to nucleoside reverse transcriptase inhibitors of HIV-2 isolates with the Q151M mutation in the reverse transcriptase. *Antivir Ther* 2005; 10(7): 861-5.
- 2/ Desbois D, Roquebert B, Peytavin G et al. In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother*. 2008 Apr;52(4):1545-8.
- 3/ Witvrouw E et al. Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: implications for treatment and postexposure prophylaxis. *Antivir Ther* 2004; 9(1): 57-65.
- 4/ Parkin NT et al. Antiretroviral drug resistance in non-subtype B, HIV-2 and SIV. *Antivir Ther* 2004; 9(1): 3-12.
- 5/ Roquebert B et al. Selection of the Q148R integrase inhibitor resistance mutation in a failing raltegravir containing regimen. *AIDS*. 2008 Oct 1;22(15):2045-6.
- 6/ Garrett N et al. Raltegravir treatment response in an HIV-2 infected patient: a case report. *AIDS* 2008, 22: 1091-1098.
- 7/ Roquebert B et al. Raltegravir Genetic Resistance Patterns in HIV-2 Infected Patients Failing Raltegravir-containing Regimen; 17th Conference on Retroviruses and Opportunistic Infection, San Francisco, CA 16-19 February 2010 (abstract 558).