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Microbiology and Immunology
Clinical and Epidemiological Virology

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Algorithm for the use of genotypic HIV-1 resistance data
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The rules include and score mutations for which *in vitro* phenotypic drug resistance or *in vivo* therapy response data have been reported, or for which retrospective associations with drug experience have been described. Some of the mutations do not necessarily result in high-level phenotypic resistance. Instead, they have been identified as key mutations along a pathway leading to high-level resistance (e.g. T215 revertants) or have proved to be predictive of therapy failure. Where supported by reliable evidence, the antagonistic or synergistic interaction effects of combinations of mutations are also incorporated (e.g. M184IV and TAMs). Three levels of interpretation criteria are applied: for HIV-1, criteria to consider an isolate as resistant, intermediately resistant or susceptible.

Genotypic susceptibility scores (GSS) are assigned to the three susceptibility levels for each drug class or individual drug. Although the same rules apply to each PI and its respective PI/r, different GSS are assigned to the boosted and un-boosted drug.

GSS	resistant	intermediate resistant	susceptible
NRTI - NtRTI	0	0.5	1
NNRTI	0	0.25	1
etravirine	0	0.5	1
PI	0	0.5	1
PI/r	0	0.75	1.5
EI	0	0.25	1
INI	0	0.25	1
dolutegravir	0	0.5	1

Target GSS for the entire treatment combination regimen are proposed. Resistance development is expected when therapy changes with GSS below the target are installed.

Clinical situation	Target GSS
Therapy-naive persons with indications of transmitted drug resistance	≥3.5
Therapy-naive and therapy-experienced persons	≥3
Therapy-experienced persons with limited treatment options	≥2

	Criteria to consider an isolate resistant [a,b,c]	Criteria to consider an isolate intermediately resistant [a,b,c]
NRTI		
zidovudine	[at least 1 mutation of (69X-XX,151M)] *or* [at least 4 mutations of (41L,67GN,69AN,70R,210W,215ACDEGHILNSVFY,219EHNQR)] *or* [3 mutations of (41L,210W,215Y) and not 184IV and not 74V] *or* [at least 3 mutations of (67GN,70R,215F,219EQ)]	[2 or 3 mutations of (41L,67GN,69AN,70R,210W,215ACDEGHILNSVFY,219EHNQR)] *or* [215ACDEGHILNSVFY and not 184IV]

didanosine	at least 1 mutation of (69DGN,69X-XX,151M) *or* [184IV and at least 1 mutation of (65RN,74IV)] *or* [at least 5 mutations of (41L,67N,70R,74IV,210W,215ACDEGHILNSVFY,219EHNQR)]	at least 1 mutation of (65NR,70EG,74IV,75T) *or* [2 mutations of (41L,215FY)] *or* [at least 3 mutations of (41L,67N,70R,210W,215ACDEGHILNSVFY,219EHNQR)]
stavudine	[at least 1 mutation of (65R, Δ67,69X-XX,75AMST,151M)] *or* [at least 4 mutations of (41L,67N,69ADGN,70R,210W,215ACDEGHILNSVFY,219EHNQR)] *or* [3 mutations of (41L,210W,215Y)]	[2 or 3 mutations of (41L,67N,69ADGN,70R,210W,215ACDEGHILNSVFY,219EHNQR)] *or* [215ACDEGHILNSVFY and not 184IV]
lamivudine	184IV *or* (65NR and 151M)	[at least 1 mutation of (65NR,Δ67,69X-XX,70EG)] *or* {[at least 1 mutation of (44AD,118I)] and [at least 3 mutations of (41L,67N,69AN,70R,210W,215ACDEGHILNSVFY,219EHNQR)]} *or* [151M and at least 3 mutations of (75I,77L,116Y)]
abacavir	[at least 1 mutation of (Δ67,69G)] *or* [at least 2 mutations of (65NR,69X-XX,74IV,115F,151M,184IV)] *or* {(69X-XX) and [at least 3 mutations of (41L,67N,70R,210W,215ACDEGHILNSVFY,219EHNQR)]} *or* {[at least 1 mutation of (65NR,74IV,115F,184IV)] and [at least 4 mutations of (41L,67N,70R,210W,215ACDEGHILNSVFY,219EHNQR]} *or* [151M and at least 2 mutations of (75I,77L,116Y)]	[1 mutation of (69X-XX,70EG,151M)] *or* {[1 mutation of (65NR,74IV,115F,184IV)] and [2 or 3 mutations of (41L,67N,70R,210W,215ACDEGHILNSVFY,219EHNQR]} *or* [at least 3 mutations of (41L,67N,70R,210W,215ACDEGHILNSVFY,219EHNQR)]
emtricitabine	184IV *or* (65NR and 151M)	[at least 1 mutation of (65NR,Δ67,69X-XX,70EG)] *or* {[at least 1 mutation of (44AD,118I)] and [at least 3 mutations of (41L,67N,69AN,70R,210W,215ACDEGHILNSVFY,219EHNQR)]} *or* [151M and at least 3 mutations of (75I,77L,116Y)]
NtRTI		
tenofovir (TDF and TAF)	69X-XX *or* (65NR and not 184IV) *or* [(41L and 210W and 215Y) and not 184IV] *or* [at least 3 mutations of (67N,70R,215ACDEGHILNSVYF,219EHNQR) and at least one mutation of (41L,210W)]	70EG *or* [65NR and 184IV] *or* [(41L and 210W and 215Y and 184IV] *or* [at least 2 mutations of (67N,70R,215ACDEGHILNSVYF,219EHNQR) and at least one mutation of (41L,210W)] *or* [151M +75I+77L+116Y]
NNRTI		
nevirapine	score is at least 2 [add 2 to the score for every mutation in the following list: 100I,101P,103HNST,106AM,181CIV,188CHL,190ACEQSTV, 230IL; add 1 to the score for every mutation in the following list: 138KQ,227CL,238NT,318F; add 0.5 to the score for every mutation in the following list: 98G,101EHNQ,103R,106I,108I,179DE,221Y]	score is at least 1 [add 1 to the score for every mutation in the following list: 138KQ,227CL,238NT,318F; add 0.5 to the score for every mutation in the following list: 98G,101EHNQ,103R,106I,108I,179DE,221Y]

efavirenz	score is at least 2 [add 2 to the score for every mutation in the following list: 100I,101P,103HNST,106M,181CIV,188CHFL,190ACEQSTV, 230IL; add 1.5 to the score for every mutation in the following list: 106A,138Q,225H; add 0.5 to the score for every mutation in the following list: 90I,98G,101EHNQ,103R,106I,108I,138K,179DE,221Y, 227CL,238NT,318F]	score is at least 1 [add 1.5 to the score for every mutation in the following list: 106A,138Q,225H; add 0.5 to the score for every mutation in the following list: 90I,98G,101EHNQ,103R,106I,108I,138K,179DE,221Y,227CL,238NT,318F]
etravirine	score is at least 3 [add 1.5 to the score for every mutation in the following list: 100I,101P,181CIV,227C,230IL; add 0.75 to the score for every mutation in the following list:138KQ,179F,190CEQSTV; add 0.5 to the score for every mutation in the following list: 101EHNQ,106I,138A,190A; add 0.25 to the score for every mutation in the following list: 90I,98G,101R,103HNST,106AM,108I,179DET,188CHFL, 221Y,225H,227L,234I,236L,238NT,318F]	score is at least 1.5 [add 1.5 to the score for every mutation in the following list: 100I,101P,181CIV,227C,230IL; add 0.75 to the score for every mutation in the following list:138KQ,179F,190CEQSTV; add 0.5 to the score for every mutation in the following list: 101EHNQ,106I,138A,190A; add 0.25 to the score for every mutation in the following list: 90I,98G,101R,103HNST,106AM,108I,179DET,188CHFL,221Y,225H,227L,234I,236L,238NT,318F]
rilpivirine	score is at least 2.5 [add 2.5 to the score for every mutation or combination of mutations in the following list: 101P,(101E+184IV),(100I+103N),(138K+184IV),181IV,188L; add 1.5 to the score for every mutation in the following list: 101E,138AGKQRS,179L,181C,221Y,227C,230IL; add 0.5 to the score for every mutation in the following list: 90I,101QT,103S,106AI,108I,179DIT,189I,190E]	score is at least 1.5 [add 1.5 to the score for every mutation in the following list: 101E,138AGKQSR,179L,181C,221Y,227C,230IL; add 0.5 to the score for every mutation in the following list: 90I,101QT,103S,106AI,108I,179DIT,189I,190E]
PI[d]		
saquinavir/r	score is at least 3.5 [add 2 to the score for every mutation in the following list: 48MV,90M; add 1.5 to the score for every mutation in the following list: 54AST,84AC; add 1 to the score for every mutation in the following list: 24I,53L,54V,71V,84V,88DS,89V; add 0.5 to the score for every mutation in the following list: 10F,20T,46IL,48A,50V,54LM,58E,71I,73STC,74SP,89T; add 0.25 to the score for every mutation in the following list: 10IV,11I,20IMRV,62V,71T,74A,82AFLMST,89I; subtract 0.25 from the score for every mutation in the following list: 50L]	score is at least 2 [add 2 to the score for every mutation in the following list: 48MV,90M; add 1.5 to the score for every mutation in the following list: 54AST,84AC; add 1 to the score for every mutation in the following list: 24I,53L,54V,71V,84V,88DS,89V; add 0.5 to the score for every mutation in the following list: 10F,20T,46IL,48A,50V,54LM,58E,71I,73STC,74SP,89T; add 0.25 to the score for every mutation in the following list: 10IV,11I,20IMRV,62V,71T,74A,82AFLMST,89I; subtract 0.25 from the score for every mutation in the following list: 50L]
indinavir/r	score is at least 3 [add 2 to the score for every mutation in the following list: 82AFST,84AV; add 1.5 to the score for every mutation in the following list: 46IL,54AST; add 1 to the score for every mutation in the following list: 10F,24I,32I,48MV,54V,76V,82M,88S,90M; add 0.5 to the score for every mutation in the following list: 20T,43T,48A,54LM,66F,71I, 73STC,74P,84C,88D,89TV,95F; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,35GN,43R,62V,71TV,74AS,89I; subtract 0.25 from the score for every mutation in the following list: 50L]	score is at least 2 [add 2 to the score for every mutation in the following list: 82AFST,84AV; add 1.5 to the score for every mutation in the following list: 46IL,54AST; add 1 to the score for every mutation in the following list: 10F,24I,32I,48MV,54V,76V,82M,88S,90M; add 0.5 to the score for every mutation in the following list: 20T,43T,48A,54LM,66F,71I,73STC,74P,84C,88D,89TV,95F; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,35GN,43R,62V,71TV,74AS,89I; subtract 0.25 from the score for every mutation in the following list: 50L]

nelfinavir	score is at least 2 [add 2 to the score for every mutation in the following list: 30N,90M; add 1.5 to the score for every mutation in the following list: 54AST,84AC,88S; add 1 to the score for every mutation in the following list: 54V,82ATF,88D; add 0.5 to the score for every mutation in the following list: 10F,20T,23I,24I,32I,43T,46IL,48AV,54LM,58E,66F,71I, 73STC,74P,76V,82LMS,84V,89TV,93M; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,33FI,35GN,43R,62V,64V,71TV,74AS,89I; subtract 0.25 from the score for every mutation in the following list: 50L]	score is at least 1.25 [add 2 to the score for every mutation in the following list: 30N,90M; add 1.5 to the score for every mutation in the following list: 54AST,84AC,88S; add 1 to the score for every mutation in the following list: 54V,82ATF,88D; add 0.5 to the score for every mutation in the following list: 10F,20T,23I,24I,32I,43T,46IL,48AV,54LM,58E,66F,71I, 73STC,74P,76V,82LMS,84V,89TV,93M; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,33FI,35GN,43R,62V,64V,71TV,74AS,89I; subtract 0.25 from the score for every mutation in the following list: 50L]
fosamprenavir/r	score is at least 3.5 [add 2 to the score for every mutation in the following list: 50V; add 1.5 to the score for every mutation in the following list: 76V,84ACV; add 1 to the score for every mutation in the following list: 47AV,48M,54MTV,82F; add 0.5 to the score for every mutation in the following list: 10F,20T,24I,32I,33F,43T,46IL,48A,54AL,58E,82AMST,89TV; add 0.25 to the score for every mutation in the following list: 10IV,20IRMV,33I,43R,48V,89I,90M; subtract 0.25 from the score for every mutation in the following list: 50L,88S]	score is at least 2 [add 2 to the score for every mutation in the following list: 50V; add 1.5 to the score for every mutation in the following list: 76V,84ACV; add 1 to the score for every mutation in the following list: 47AV,48M,54MTV,82F; add 0.5 to the score for every mutation in the following list: 10F,20T,24I,32I,33F,43T,46IL,48A,54AL,58E,82AMST,89TV; add 0.25 to the score for every mutation in the following list: 10IV,20IRMV,33I,43R,48V,89I,90M; subtract 0.25 from the score for every mutation in the following list: 50L,88S]
lopinavir/r	score is at least 3.5 [add 2 to the score for every mutation in the following list: 47A; add 1.5 to the score for every mutation in the following list: 32X-X,50V,54AT,76V; add 1 to the score for every mutation in the following list: 47V,48M,54SV,82FS,84A; add 0.5 to the score for every mutation in the following list: 10F,20T,24FI,32I,33F,43T,46IL,48AV,53L,54LM, 71I,73STC, 82ALMT,84V,88D,90M; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,33I,43R,64MV,71TV,77ATV; subtract 0.25 from the score for every mutation in the following list: 50L]	score is at least 2 [add 2 to the score for every mutation in the following list: 47A; add 1.5 to the score for every mutation in the following list: 32X-X,50V,54AT,76V; add 1 to the score for every mutation in the following list: 47V,48M,54SV,82FS,84A; add 0.5 to the score for every mutation in the following list: 10F,20T,24FI,32I,33F,43T,46IL,48AV,53L,54LM, 71I,73STC, 82ALMT,84V,88D,90M; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,33I,43R,64MV,71TV,77ATV; subtract 0.25 from the score for every mutation in the following list: 50L]
atazanavir(/r)	score is at least 3.5 [add 2 to the score for every mutation in the following list: 48MV,50L; add 1.5 to the score for every mutation in the following list: 54AST,88S; add 1 to the score for every mutation in the following list: 10Y,20T,47V,54V,74P,82LT,84V,88D,90M; add 0.5 to the score for every mutation in the following list: 10F,24I,32I,46IL,54LM,58E,71IL,73ACFST,82AMSF,85V; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,33FI,71TV,74AS; subtract 0.25 from the score for every mutation in the following list: 76V]	score is at least 2 [add 2 to the score for every mutation in the following list: 48MV,50L; add 1.5 to the score for every mutation in the following list: 54AST,88S; add 1 to the score for every mutation in the following list: 10Y,20T,47V,54V,74P,82LT,84V,88D,90M; add 0.5 to the score for every mutation in the following list: 10F,24I,32I,46IL,54LM,58E,71IL,73ACFST,82AMSF,85V; add 0.25 to the score for every mutation in the following list: 10IV,20IMRV,33FI,71TV,74AS; subtract 0.25 from the score for every mutation in the following list: 76V]
tipranavir/r	score is at least 3.5 [add 2 to the score for every mutation in the following list: 47V, 74P,82T; add 1.5 to the score for every mutation in the following list: 58E,82LS,83D; add 1 to the score for every mutation in the following list:: 41T,43T,54AMV,84ACV; add 0.5 to the score for every mutation in the following list: 33F,47A,46L,54ST; add 0.25 to the score for every mutation in the following list: 32I,38W,45I,71L,73T,82AFM,89TV,90M; subtract 0.25 from the score for every mutation in the following list: 50LV]	score is at least 2 [add 2 to the score for every mutation in the following list: 47V, 74P,82T; add 1.5 to the score for every mutation in the following list: 58E,82LS,83D; add 1 to the score for every mutation in the following list:: 41T,43T,54AMV,84ACV; add 0.5 to the score for every mutation in the following list: 33F,47A,46L,54ST; add 0.25 to the score for every mutation in the following list: 32I,38W,45I,71L,73T,82AFM,89TV,90M; subtract 0.25 from the score for every mutation in the following list: 50LV]

darunavir/r	score is at least 3.5 [add 1.5 to the score for every mutation in the following list: 50V,76V,84ACV; add 1 to the score for every mutation in the following list: 32I,47AV,54LM,; add 0.5 to the score for every mutation in the following list: 11I, 33F, 74P, 89V; add 0.25 to the score for every mutation in the following list: 89I, 46I; subtract 0.25 from the score for every mutation in the following list: 50L,88S, 82AST]	score is at least 2.5 [add 1.5 to the score for every mutation in the following list: 50V,76V,84ACV; add 1 to the score for every mutation in the following list: 32I,47AV,54LM,; add 0.5 to the score for every mutation in the following list: 11I, 33F, 74P, 89V; add 0.25 to the score for every mutation in the following list: 89I, 46I; subtract 0.25 from the score for every mutation in the following list: 50L,88S, 82AST]
darunavir/c	score is at least 3.5 [add 1.5 to the score for every mutation in the following list: 50V,76V,84ACV; add 1 to the score for every mutation in the following list: 32I,47AV,54LM,; add 0.5 to the score for every mutation in the following list: 11I, 33F, 74P, 89V; add 0.25 to the score for every mutation in the following list: 89I, 46I; subtract 0.25 from the score for every mutation in the following list: 50L,88S, 82AST]	score is at least 2.5 [add 1.5 to the score for every mutation in the following list: 50V,76V,84ACV; add 1 to the score for every mutation in the following list: 32I,47AV,54LM,; add 0.5 to the score for every mutation in the following list: 11I, 33F, 74P, 89V; add 0.25 to the score for every mutation in the following list: 89I, 46I; subtract 0.25 from the score for every mutation in the following list: 50L,88S, 82AST]
EI		
enfuvirtide	score is at least 2 [add 1 to the score for every mutation in the following list: 36DESV,38AEM,40H,41R,42DEHKQT,43DKQS,44MV, 45MPQ]	score is at least 1 [add 1 to the score for every mutation in the following list: 36DESV,38AEM,40H,41R,42DEHKQT,43DKQS,44MV, 45MPQ]
maraviroc [e]	[(CXCR4-tropic or D/M tropic) by ES Trofile™] or [(X4 or R5X4) by the clonal interpretation of geno2pheno with false positive rate of 10% using V3 loop triplicate population sequences or 20% using V3 loop single population sequence]	
INI		
raltegravir	score is at least 2 [add 2 to the score for every mutation in the following list: 143CHKRS,148HKR, 155HST add 1 to the score for every mutation in the following list: 66K,92QV,118R,121Y,140ACS,151L add 0.5 to the score for every mutation in the following list: 74M,97A,138A,163K add 0.25 to the score for every mutation in the following list: 138K,163R,119R,151I,157Q,230NR,263K]	score is at least 1 and less than 2 [add 1 to the score for every mutation in the following list: 66K,92QV,118R,121Y,140ACS,151L add 0.5 to the score for every mutation in the following list: 74M,97A,138A,163K add 0.25 to the score for every mutation in the following list: 138K,163R,119R,151I,157Q,230NR,263K]
elvitegravir	score is at least 2 [add 2 to the score for every mutation in the following list: 66AIK,92QG,145S,146ILPR,147G,148HKR,155HST; add 1 to the score for every mutation in the following list: 121Y,140ACS,151AL; add 0.5 to the score for every mutation in the following list: 51Y,97A,114Y,146K,153FY,263K]	score is at least 1 and less than 2 [add 1 to the score for every mutation in the following list: 121Y,140ACS,151AL; add 0.5 to the score for every mutation in the following list: 51Y,97A,114Y,146K,153FY,263K]

dolutegravir	score at least 2 [add 2 to the score for every mutation in the following list: (49G + 230R + 263K) add 1.5 to the score for every mutation in the following list: (148HKR + 74I); add 1 to the score for every mutation in the following list: 148HKR, 118R, 263K add 0.5 to the score for every mutation in the following list: 66K, 74M, 92Q, 140ACS, 151L, 153FY, 155HST add 0.25 to the score for every mutation in the following list: 49GP, 97A, 121Y, 147G, 230GR]	score at least 1.5 and less than 2 [add 1.5 to the score for every mutation in the following list: (148HKR + 74I); add 1 to the score for every mutation in the following list: 148HKR, 118R, 263K add 0.5 to the score for every mutation in the following list: 66K, 74M, 92Q, 140ACS, 151L, 153FY, 155HST add 0.25 to the score for every mutation in the following list: 49GP, 97A, 121Y, 147G, 230GR]

[a] T69X-XX, X whatever amino acid. ∆67, deletion of amino acid 67. A, alanine; R, arginine; N, asparagine; D, aspartic acid; C, cysteine; Q, glutamine; E, glutamic acid; G, glycine; H, histidine; I, isoleucine; L, leucine; K, lysine; M, methionine; F, phenylalanine; P, proline; S, serine; T, threonine; W, tryptophan; Y, tyrosine and V, valine. [b] If more mutations are present at a certain position (e.g. T215Y and T215F), they are only counted as one mutation in the rules and the maximum score at that particular position is considered. [c] If none of the criteria to consider an isolate resistant towards a particular drug are full-filled, proceed to the criteria to consider an isolate intermediately resistant. If none of the latter criteria are full-filled, the isolate can be scored susceptible to that particular drug. [d] r, PI boosted with baby dose of ritonavir. NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EI, entry inhibitor; INI, integrase inhibitor. [e] For genotypic prediction of co-receptor usage we refer to http://coreceptor.bioinf.mpi-inf.mpg.de/index.php (Sing T. et al. Predicting HIV co-receptor usage based on genetic and clinical covariates. Antiviral Therapy, 2007). For phenotypic prediction of co-receptor usage we refer to the Enhanced Trofile™ assay (Monogram Biosciences) http://trofileassay.com.