I

Reviews

Sequence Alignment in HIV Computational Analysis 2
Ana Abecasis, Anne-Mieke Vandamme, Philippe Lemey

The Epidemiology of Transmission of Drug Resistant HIV-1 17
David A.M.C. van de Vijver, Annemarie M.J. Wensing, Charles A.B. Boucher

Search Tools in the HIV Databases 37
Jennifer Macke, Charles Calef, Karina Yusim, Robert Funkhouser, Thomas Leitner, James Szinger, Brian Gaschen, Werner Abfalterer, John Mokili, Brian Foley, Bette Korber, Carla Kuiken

Mutations in Retroviral Genes Associated with Drug Resistance 58
Shauna A. Clark, Charles Calef, John W. Mellors

Sequence Alignment in HIV Computational Analysis

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Introduction

Aligning nucleotide or amino acid sequences is a very common procedure in HIV computational analysis. An accurate alignment is the first step in making a proper and correct analysis of HIV datasets. Sequence alignments are essential for phylogenetic analysis tracing the epidemiology of HIV, but also for interpretations of drug resistance and data mining efforts, where correctly positioning nucleotides or amino acids of different strains with respect to each other is pivotal.

Positional homology

If two sequences have a common ancestor, they are said to be homologous. By aligning them, we are inferring positional homology from statistically significant sequence similarity: any two sequences have some measurable similarity, but a statement of homology implies that this similarity is a specific result of common ancestry (47). Only when the common ancestry is recent enough, homology will still be reflected in a sufficient similarity, allowing an unambiguous alignment. When we align sequences, we are therefore looking for evidence that they have diverged from a common ancestor by evolutionary processes like selection and mutation (substitutions, insertions, and deletions) (9). Hence, the process of alignment is intimately related to inference of evolutionary relationships among sequences. In fact, the ideal alignment algorithm would allow us to co-estimate sequence alignment and phylogeny.

It is not surprising that the quality of an alignment will depend on the degree of sequence divergence, in particular the frequency of insertions and deletions (collectively referred to as indels) that have occurred. In HIV sequences, indels are frequently observed, even at relatively low divergence or over short evolutionary times. Figure 1a shows a short amino acid alignment of HIV envelope sequences sampled from a single host (positions 346 to 416 in gp120 according to HXB2 numbering). The sequences were obtained from plasma and different cellular populations at two different time points separated by approximately two years (51). Although this represents only a relatively short evolutionary time, the sequences cannot be unambiguously aligned in the hypervariable loop (V4). This example illustrates that any alignment procedure will generate an output for which the quality cannot be guaranteed. Obviously, alignment quality becomes even more problematic at greater evolutionary scales. For other viruses like Hepatitis C (HCV), indels may be observed less frequently relative to nucleotide substitutions, making the alignment process more straightforward.

Any two sequences can be fed into an alignment algorithm, and an alignment will be provided. When such an alignment requires many indels, and the aligned nucleotides do not seem to be unambiguously aligned, such an alignment cannot be considered successful in achieving positional homology. Some general guidance in assessing alignment quality can be found in the overall sequence similarity: the “twilight zone” between unambiguous and ambiguous alignment is considered to lie between 50% and 60% sequence identity for nucleotide sequences (14), and between 10% and 20% sequence identity for amino acids sequences (61).

Global versus local alignments

Needleman and Wunsch (39) published the first global alignment algorithm in 1970. Global alignment algorithms aim at aligning the entire sequence of two potentially homologous regions, as opposed to local alignment algorithms, which align only regions of high similarity. The first local alignment algorithm using dynamic programming was developed by Smith and Waterman (56) as a variation of the Needleman-Wunsch algorithm. The main difference of the Smith-Waterman algorithm is that the alignment can end anywhere in the matrix. By matrix, we refer to the two-dimensional array where we

Fig 1a

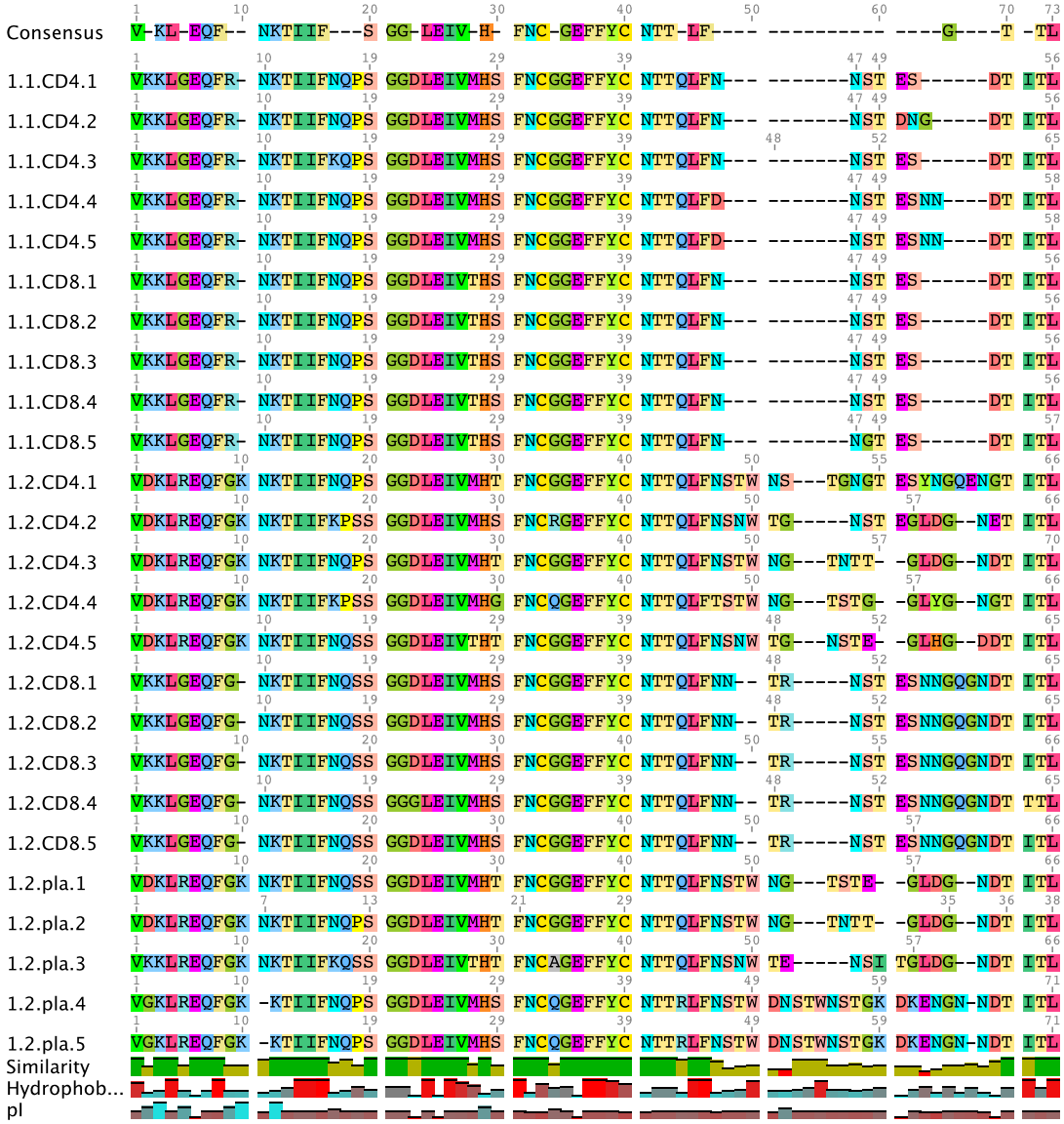
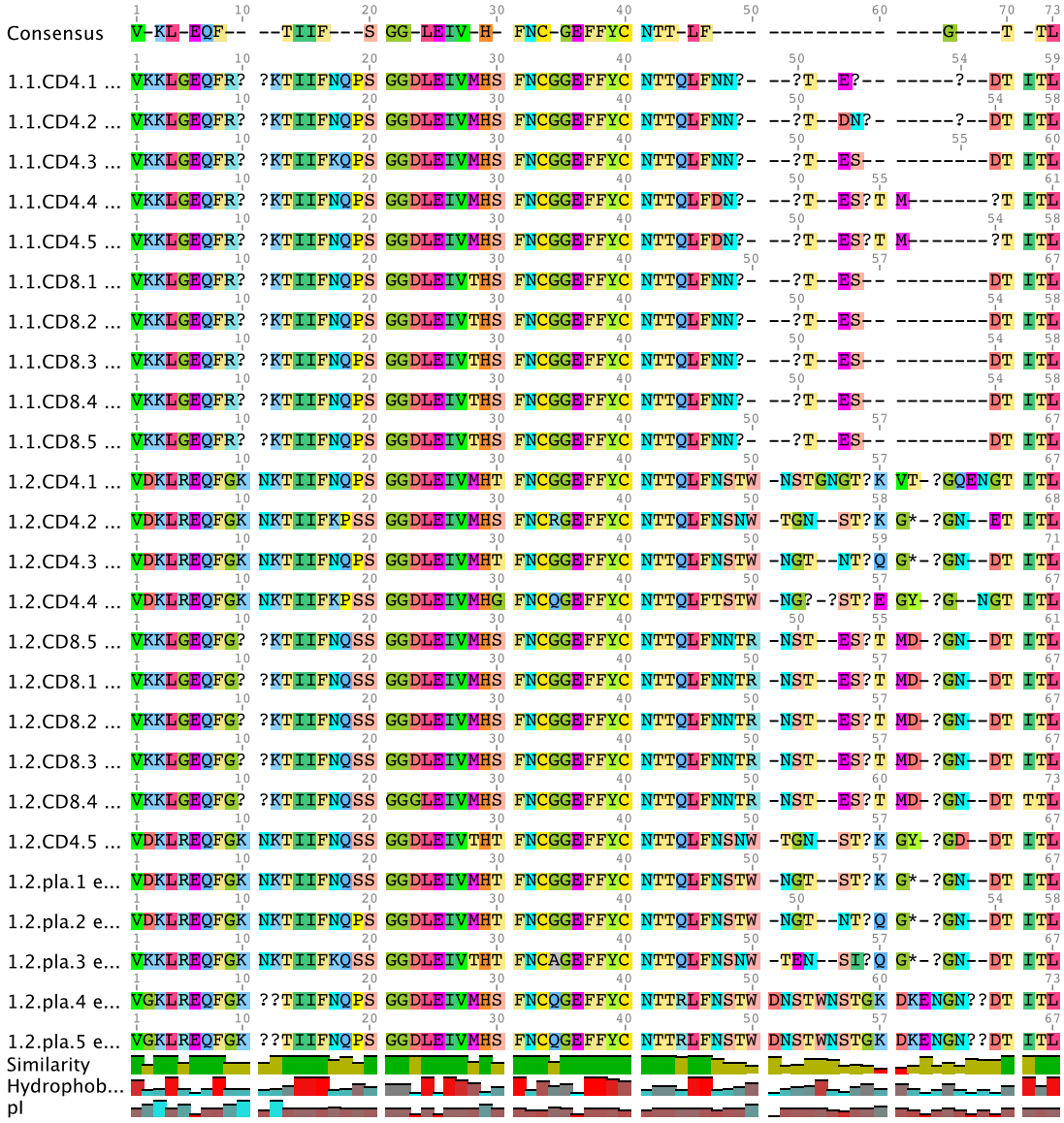


Figure 1 - Amino acid alignment of HIV-1 envelope sequences sampled from a single host. a) ClustalW output (default settings) for the aligned amino acid sequences.

can score identities and differences between two sequences (see Figure 2b). By allowing the alignment to end anywhere in the matrix, only the more similar subsequences of the sequences are aligned. Local alignment is the most sensitive procedure to detect similarity when comparing highly divergent sequences and is therefore very useful for finding common domains between protein sequences or for comparing extended sections of genomic DNA sequences (9). For details on these algorithms, we refer to the original papers (39, 56), books (28, 47), and reviews (49). General descriptions and exercises can also be found in chapter 3 of "The Phylogenetic Handbook" (21), which focuses mainly on global multiple alignment strategies and software.

Fig 1b



b) ClustalW output (default settings) for the aligned nucleotide sequences, translated to amino acid. The pdf images of the alignments were generated using Geneious v2.5.3.

Pairwise alignments

Global pairwise alignment

Global pairwise alignment is, as mentioned above, achieved through the use of the Needleman and Wunsch algorithm (39). This algorithm assumes that the two sequences are similar enough over their entire length to generate a good alignment. In the nucleotide alignment matrix, a positive score is given if there is a match between the sequences and a score of 0 if there is a mismatch. If there is a need to include gaps in the alignment, gap-opening and gap-extending penalties are accounted for in the alignment score. As part of the dynamic programming procedure, the entries of the alignment matrix are computed recursively using the forward algorithm. The back-tracing algorithm is subsequently used to find the best-scoring alignment, starting from the $(n1,n2)^{th}$ position of the matrix and finishing at the $(0,0)^{th}$ position, where n1 and n2 are the lengths of sequences 1 and 2, respectively (see Figure 2) (35, 39, 47).

Local pairwise alignment

It is common practice to compare a query sequence to a database of sequences, in order to find the most similar and potentially homologous sequences. The use of this technique can also assist in quality control of sequencing, by identifying potential lab contaminations, or in compiling an appropriate dataset for further evolutionary studies.

The Smith-Waterman algorithm implements a very straightforward variation of the Needleman-Wunsch algorithm, which is to replace the overall score of the alignment by zero if it takes on negative values for all alternative pathways. This simple approach restricts alignment to regions of reasonably high similarity. How this differs from global alignment is illustrated in the grey box of Figure 2a. Exact alignment algorithms are so computationally expensive that they become unrealistically slow if one wants to compare a sequence to a background database of sequences. To overcome this limitation to database applications, heuristic alignment algorithms have been developed. The most widely used local

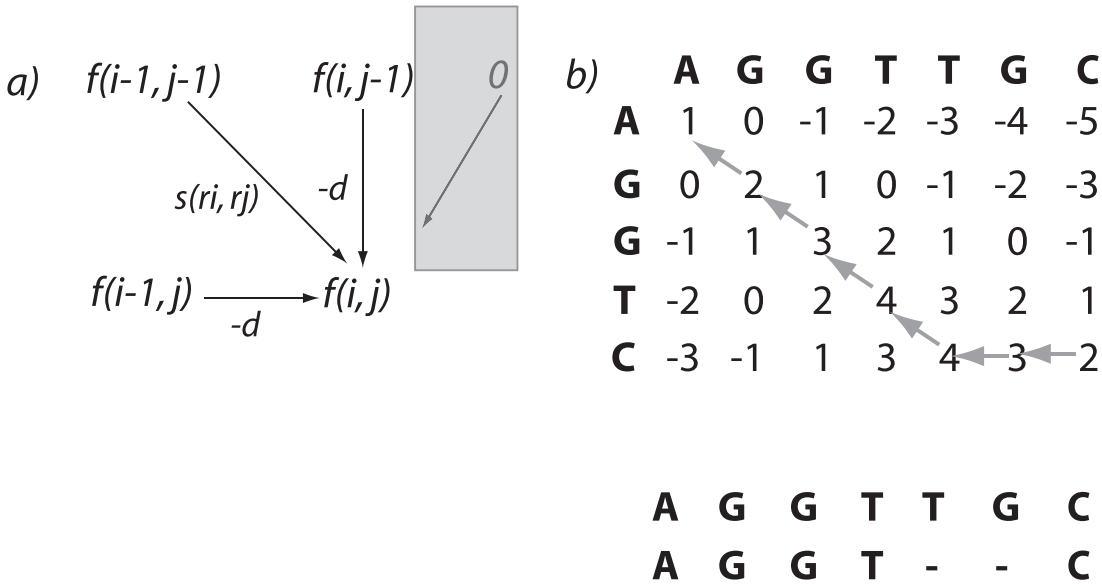


Figure 2 - a) Forward algorithm of the Needleman and Wunsch algorithm to recursively compute the entries of the alignment matrix. The grey box represents the additional parcel of the Smith Waterman algorithm (adapted from (35)) b) Example of an alignment matrix and the back-tracing algorithm used to find the best-scoring alignment.

alignment search tools are BLAST (1) and FASTA (48). The BLAST programs are available at the NCBI website (http://www.ncbi.nlm.nih.gov/BLAST/). The FASTA programs are available at the EMBL-EBI website (http://www.ebi.ac.uk/fasta/). In both cases, the search tool can be used online or downloaded as standalone software to a local computer. The advantage of downloading any of these packages to a local computer is that one can search against a local background database of sequences. This can be very useful if one is interested in searching only against a specific set of sequences. Furthermore, the Los Alamos HIV database (http://www.hiv.lanl.gov/) implements an HIV-BLAST program, which can either use the whole Los Alamos HIV database (default) or a user-defined database as background.

BLAST is usually preferred over FASTA since it is generally faster and more sensitive (because BLAST, in contrast to FASTA, does not require a perfect match in the first step). However, FASTA has been shown to generally perform better than BLAST in terms of mean average precision. For both methods, the search quality appears to be proportional to the logarithm of search time (3).

Multiple sequence alignments

Multiple sequence alignment involves global alignment of more than two sequences. Given that pairwise alignment tries to find the best path in a matrix, multiple sequence alignment can be conceived as a multidimensional problem. A naïve solution to this problem has complexities concerning computation time and memory, which are prohibitively large for real-world alignments (37). The most commonly used heuristic approach to multiple sequence alignment is the 'progressive alignment' algorithm, as originally referred to by Feng and Doolittle (12). Although there are several different progressive alignment strategies (23, 25, 57), the heuristic for aligning the most similar pairs of sequences first is crucial for their performance. Most strategies start from pairwise alignments and use the pairwise similarities to build quick guide trees, thereby reducing the problem of multiple alignment to a set of pairwise alignments (with one alignment at each internal node of the guide tree). This strategy relies on the evolutionary principle that the insertion of gaps should be more straightforward for more closely related sequences. The ideal alignment will be the one that maximizes the sum of similarities for all pairs of sequences. Progressive alignment algorithms generate fast and, in most cases, reasonably accurate results. However, a heuristic algorithm does not guarantee retrieval of the best alignment (42).

Multiple alignment software

We provide a detailed listing of software implementing different alignment algorithms in Table 1, but our discussion below will focus on the most popular or useful programs for HIV according to our experience.

Clustal

The most widely used multiple alignment programs are ClustalW (59) and ClustalX (58). In the Clustal algorithm, sequences are aligned in pairs to generate a distance matrix that can be used to make a rough initial tree of the sequences; this rough tree is used to progressively create the multiple alignment according to the branching order in the guide tree (21, 59). ClustalW is a command-line based software, available for Unix, MacOsX, and Windows operating systems. ClustalX uses the same alignment algorithm and has more or less the same features as ClustalW, but has a graphical interface and is considered to be more user-friendly. The Clustal algorithm is implemented in many alignment editing software packages.

T-Coffee

The T-Coffee multiple alignment software implements an algorithm that combines progressive and consistency-based alignment (44), and is available for online usage (http://www.ch.embnet.org/software/TCoffee.html) or for download (http://www.tcoffee.org/Projects_home_page/t_coffee_home_page.html). Because it considers information included in a library of pairwise alignments between the input sequences, the algorithm has been reported to be more accurate than ClustalW (see below). Hence, it is considered to be useful for alignments of more divergent sequences. T-Coffee,

Table 1 Software implementing different alignment algorithms for multiple sequence alignment.
Abbreviations: AA = amino acid, NA = nucleic acid, OS = operating system, WI = Web interface, v = version. All these software packages are available as freeware.

Name	AA/NA Both	Ref.	Algorithm	Website	Supported OS Win	Linux	Mac
ABA	AA	(53)	Progressive/A-Bruijn graphs	http://nbcr.sdsc.edu/euler/aba_v1.0/		X	X
ClustalW	Both	(59)	Progressive	http://bips.u-strasbg.fr/fr/Documentation/ClustalX/	X	X	X
DiAlign	Both	(38)	Consistency-based/Iterative	http://bibiserv.techfak.uni-bielefeld.de/dialign/	X	X	X
MAFFT	Both	(27)	Progressive/iterative	http://align.bmr.kyushu-u.ac.jp/mafft/software/	X	X	X
MSA	Both	(34)	Exact (Carrillo-Lipman optimal alignment algorithm)	http://www.ncbi.nlm.nih.gov/CBBresearch/Schaffer/msa.html		X	
MultAlign (WI)	Both	(5)	Progressive	http://bioinfo.genopole-toulouse.prd.fr/multalin/multalin.html	X	X	X
MUSCLE	Both	(10)	Progressive/Iterative	http://www.drive5.com/muscle/	X	X	X
PileUp (algorithm implemented in SeqLab see Table 2)	Both	(24)	Progressive	http://www.accelrys.com/products/gcg/	-	-	-
POA (WI: POAVIZ or POA v2 for download)	Both	(32)	Progressive (Partially-ordered graphs)	http://www.bioinformatics.ucla.edu/poa		X	
PROBCONS (1.10-1 for download or WI)	AA	(7)	Consistency-based/Probabilistic modeling	http://probcons.stanford.edu/about.html	X	X	X
ProDA (v1.0)	AA	(50)	Progressive/Consistency-based	http://proda.stanford.edu	?	X	X
PRRP (WI)	Both	(16)	Iterative/Stochastic	http://prrn.hgc.jp/	X	X	X
SAGA (v0.95)	AA	(43)	Iterative/Stochastic/GA	http://www.tcoffee.org/Projects_home_page/saga_home_page.html		X	
SAM (v3.5)	AA	(29)	Iterative/Stochastic/HMM	http://rph@cse.ucsc.edu		X	
T-Coffee (v5.03 for download or WI)	Both	(44)	Consistency-based/Progressive	http://www.tcoffee.org/Projects_home_page/t_coffee_home_page.html	X	X	X

however, has the disadvantage of being much more time- and memory-consuming. A recent version of this algorithm can also incorporate three-dimensional structural information for the alignment of protein sequences (45).

MAFFT and MUSCLE

The alignment algorithms implemented in MAFFT and MUSCLE are also considered to have good performance characteristics (10, 26). These include variations of the progressive alignment method, which make the multiple alignment process faster than ClustalW and, in some cases, also more accurate (11) (63).

ProbCons

According to Wallace et al., the currently most accurate method for multiple sequence alignment is ProbCons (63). This method uses a pair-hidden Markov Model to specify the probability distribution over all alignments between a pair of sequences. The expected accuracy function is used as a measure of similarity to build the guide tree, and the novel probabilistic consistency scoring function is used for scoring the multiple alignments. However, the reported high accuracy of this method is achieved at the cost of computation time (7).

Comparison of multiple alignment programs

As shown in Table 1, various algorithms for multiple sequence alignment are now available. Independent evaluation of different alignment algorithms has therefore become an important issue. The database mainly used for this type of evaluation is BAliBASE - Benchmark Alignment dataBASE for the evaluation of multiple alignment programs (62). This database was created in 1999 and has since been improved; the current version is BaliBASE v3.0 (60). The alignments included in BAliBASE are divided into four hierarchical reference sets. Each of the main sets may be further subdivided into smaller groups, according to sequence length and percent similarity. The multiple alignments included in BAliBASE were manually refined and therefore constitute an ideal reference alignment set for comparison with the alignments being evaluated (62) (http://bips.u-strasbg.fr/fr/Products/Databases/BAliBASE/).

To our knowledge, only two papers have been published that independently compare the performance of different algorithms for multiple alignments using BAliBASE. The first paper was published in 1999 and compares the performance of 10 different alignment algorithms: PRRP, ClustalX, SAGA, DiAlign, SB_PIMA, ML_PIMA, MultAlign, PileUp, MULTAL and HMMT.

In the BAliBASE, there are two reference sets that might be interesting for the analysis of the performance of these algorithms for HIV-1 datasets: one of the reverse transcriptase family (1rthA) and another of HIV-1 protease (1fmb). Both are included in reference 1, in the group of alignments with more than 35% identity. The first is included in the subgroup of long sequences and the second in the subgroup of short sequences. In these groups, there were no significant differences reported between the alignment algorithms studied. However, it is shown that the performance clearly decreases with the decrease of percent identity and with shorter sequence lengths. Considering the individual results of the two above-mentioned datasets, ClustalX and PileUp presented a slightly higher score than the other algorithms in the 1rthA dataset, while ClustalX, SAGA, MultAlign and PileUp seem to perform better in the 1fmb dataset (http://bips.u-strasbg.fr/fr/Products/Databases/BAliBASE/prog_scores.html) (61).

A more recent study by Lassman et al. compared the performance of Poa, DiAlign, T-Coffee and ClustalW. The general conclusion of this paper was that T-Coffee and DiAlign performed better than Poa and ClustalW. However, the differences were only marginal, and ClustalW performed better than DiAlign in the group where 1fmb and 1rthA datasets are included. Poa generally performed worse, but has the advantage of being much faster than the other algorithms (31).

Alignment of protein vs nucleotide sequences

It is well known that at high divergence the ‘signal-noise ratio’ in protein sequences is much better than in nucleotide sequences. Two random nucleotide sequences of equal base composition will be 25%

identical if gaps are not allowed and 50% identical if gaps are allowed (46). This situation may obscure any genuine relationship of homology that may exist at high sequence divergence (46). In addition, amino acid alignments preserve the reading frame of coding sequences, and they also employ more informative scoring matrices, which can increase the quality of the alignment of coding sequences. The example in Figure 1 illustrates the difference between amino acid sequences (Figure 1a) and nucleotide sequences (Figure 1b) as output for a multiple alignment program like ClustalW. In the second case, the information about the reading-frame was lost in the region between 50–70 aa, as seen by the incomplete codons (?) and stop codons (*) present in the alignment.

Despite this advantage, researchers often like to perform further analyses on the protein coding sequences. In this context, the software RevTrans is extremely useful. The program takes as input a set of unaligned nucleotide sequences, translates it, constructs a multiple alignment of the amino acid sequences, and finally builds a multiple alignment of nucleotide sequences by 'reverse translation' of the amino acid alignment (64). This software is available online (http://www.cbs.dtu.dk/services/RevTrans). DAMBE can also be useful for this purpose (see below).

The amino acid scoring matrices have usually been derived from mammalian genome alignments, and their applicability to HIV proteins is not well studied. The development of empirical HIV scoring matrices could therefore be a significant advance in accurately aligning HIV sequences.

Handling gaps

One of the most important problems in editing alignments is handling gaps. Gaps need to be inserted for various reasons, such as indels, sequencing errors, or simply due to different lengths of the sequences. Methods used to infer evolutionary distances can deal with gaps in two different ways: one is to ignore all sites that include gaps or missing data (complete deletion), and the other way is to compute a distance for each pair of sequences, ignoring only gaps involved in the two sequences being compared (pairwise deletion). This second option can be useful if the number of nucleotides involved in the gaps is small and if gaps are distributed randomly in the alignment (40). In likelihood-based phylogenetics, gaps are usually treated as missing data, and maximum likelihood computations average over every possible character state.

The decision on how to treat gaps in an alignment is not always straightforward. Gaps at the beginning or end of the alignment (due to different lengths of the sequences) can be removed by trimming the alignment to the same length. Gap columns in the middle of the alignment can also be removed from the final alignment. However, if a few sequences are much shorter than others or include many gaps, it might not be a good option to include them in the analysis, since a lot of information might be ignored. Therefore, two alternative strategies can be used avoid this: one is to exclude those sequences from the alignment if they are not absolutely necessary for the analysis; the other is to replace each gap in those sequences by the "missing" character (in most software this is represented by a "?") (22).

A good rule of thumb in deciding on what to do with a gap column is to exclude columns where 50% or more of the sequences of the alignment are gapped, while keeping columns where less than 50% of the sequences are gapped.

Alignment editors

Algorithmic alignment does not necessarily retrieve the best alignment. It is important to always verify whether the sequence data are aligned unambiguously and, if necessary, manually correct the alignment. For this purpose, alignment editing software packages are extremely important. A detailed review of all the software for alignment edition, visualization, and presentation is available online at the webpage of the Pasteur Institute (http://bioweb.pasteur.fr/cgi-bin/seqanal/review-edital.pl). We present an extensive listing of available alignment editors in Table 2. We also selected the software that we consider more useful for manual editing of HIV-1 multiple alignments to discuss in more detail below. We selected programs based on their user-friendliness, the availability of additional features, and their availability for Windows, Linux, and MacOsX operating systems. We describe BioEdit, DAMBE, Se-Al, GeneDoc, JalView, Geneious, and GDE.

Table 2 Overview of programs for alignment editing. All are freeware with the exceptions of Gene Studio Pro and SeqLab. The academic version of Geneious is free, but doesn't allow alignment editing. The commercial Pro version allows manual alignment editing, ClustalW, and profile alignment. Chromas Lite is a simpler version of Chromas, available free of charge. Chromas can be downloaded for free, but only for a 60-day period.

		Supported operating systems			Input formats													
Editor (version)	Website	Win	Linux	Mac	GenBank	fasta	phylip	nexus	mega	clustal	NBRF pir	GCG msf	RSF	DNAstar	EMBL/Swissprot	GDE	PFAM	DNAstrider	PAML
AnnHyb (4.936)	http://www.bioinformatics.org/annhyb/	X	X			X							X		X				
Base-by-base	http://athena.bioc.uvic.ca/workbench.php?tool=basebybase&db=	X	X	X	X	X				X					X				
BioEdit (7.0.5)	http://www.mbio.ncsu.edu/BioEdit/bioedit.html	X			X	X	X	X		X	X	X		X	X			X	
CINEMA (5)	http://www.biochem.ucl.ac.uk/bsm/dbbrowser/CINEMA2.02/index2.html		X								X								
Chromas (2.31)	http://www.infobiogen.fr/services/analyseq	X			X					X		X							
DAMBE (4.5.24)	http://dambe.bio.uottawa.ca/dambe.asp	X			X	X	X	X	X	X	X	X			X			X	X
DNA Stacks (1.3.4)	http://biology.fullerton.edu/deernisse/dnastacks.html			X	X	X	X	X		X			X		X				
GDE (2.2)	http://www.bioafrica.net/GDElinux/index.html		X	X	X	X	X	X		X	X	X	X			X		X	
Se-Al (2.0a11)	http://evolve.zoo.ox.ac.uk/software.html?name=Se-Al			X		X	X	X			X					X			
GeneDoc (2.6.03)	http://www.psc.edu/biomed/genedoc/	X				X				X	X	X							
Geneious (2.5.3)	http://www.geneious.com/	X	X	X	X	X		X	X	X		X	X	X				X	
GeneStudio Pro (2.0.6.3)	http://www.genestudio.com/genestudio.htm	X			X	X	X	X		X	X	X		X	X	X		X	
JalView (2.2)	http://www.jalview.org/	X	X	X		X				X	X	X					X		
JaMBW (1.1)	http://www.infobiogen.fr/services/analyseq	X	X	X	X	X					X				X				
JevTrace (3.12b)	http://www.cmpharm.ucsf.edu/%7Emarcinj/JEvTrace/index.html	X	X	X		X				X			X						
MUST 2000	http://www.isem.univ-montp2.fr/PPP/PM/RES/Info/@Softwares.php#MUST2000	X			X						X				X				
ProMSED (2)	ftp://ftp.ebi.ac.uk/pub/software/dos/promsed/	X				X				X	X	X	X		X		X		
SeaView	http://pbil.univ-lyon1.fr/software/seaview.html	X	X	X		X	X	X		X		X							
GCG/SeqLab	http://www.accelrys.com/products/gcg/	X	X	X	X	X					X				X				
SeqPup (0.9)	http://iubio.bio.indiana.edu/soft/molbio/seqpup/java/seqpup-doc.html	X	X	X	X	X	X	X		X	X	X			X			X	
W2H (4.1.2) (web interface)	http://www.w2h.dkfz-heidelberg.de/	X	X	X	X	X					X				X				

BioEdit

BioEdit is a manual alignment editor available for Windows. It includes many analysis tools for sequences/alignments and allows several external tools to be configured to run through the BioEdit interface. Examples of the external tools that can be run through the BioEdit interface are TreeView, BLAST, and ClustalW. Many other useful features are incorporated into BioEdit, such as the ability to obtain consensus sequences, amino acid and nucleotide composition statistics, entropy plots, hydrophobicity profiles, and dot plots of pairs of sequences. The last update of BioEdit was in May 2005 (v7.0.5), but it is still available online for download (see Table 2 for link)(19).

DAMBE

DAMBE (Data Analysis in Molecular Biology and Evolution) is an integrated Windows program for descriptive and comparative analysis of molecular data. It has features for manipulating, editing, and converting sequences and alignments in different formats. One of the most interesting features of DAMBE is its ability to align protein-coding nucleotide sequences against aligned amino acid sequences, which avoids frame-shifts typical for alignments of HIV nucleotide sequences (see Figure 1b). In addition, DAMBE can compute statistics for nucleotide, amino acid, and codon frequencies, as well as codon usage and amino acid usage bias. Moreover, the program implements several comparative sequence analysis features: quantification of substitution patterns and fitting statistical distributions to among-site substitution rate heterogeneity, therefore helping in the selection of a substitution model; phylogenetic reconstruction based on distance, maximum-parsimony and maximum-likelihood methods with the option to perform bootstrapping and jackknifing; testing alternative phylogenetic hypotheses; phylogenetic tree viewing and manipulation; and graphical tools as well as formal tests to evaluate the phylogenetic signal of a dataset (65).

Se-Al

Se-Al is a very straightforward and user-friendly software strictly focused on alignment editing, visualization, and file format conversion. It allows easy toggling between nucleotide reading frames, codons, and amino acids, and presents sequences with appropriate coloring, allowing interactive editing of the sequence alignment. Thanks to editing features like selecting and sliding individual residues or blocks of sequence stretches, and cutting and pasting, which can be performed with the usual MacOS short keys, it is an easy and flexible tool for manually editing alignments. Other useful Se-Al features are the ability to generate consensus sequences, switching between reverse, complement and reverse-complement of selected sequences, selecting site ranges, and several gap deletion options (52).

GeneDoc

GeneDoc provides tools for visualizing, editing, and analyzing multiple sequence alignments. The program can incorporate structural or biochemical information as guidance to which residues should be aligned, and secondary structures can be easily visualized. GeneDoc can perform pairwise alignment and multiple sequence alignment, and allows the user to compute the score of the alignment for any selected fragment. GeneDoc also provides some additional analysis tools, which can be useful for grouping sequences in the alignment. These include the Kolmogorov-Smirnov tests of distributions of alignment scores or comparisons of sequences in terms of the percentage of identities between a pair of aligned sequences. A positive result in the test of whether the scores for pairs of sequences within the same group are smaller than the scores for pairs of sequences that are in different groups would indicate that the grouping categories are systematically reflected in the sequences (41).

JalView

In addition to the general viewing and editing features of JalView, the program has several useful features for the analysis of sequences or alignments. JalView is one of the few programs that can realign sequences using three different alignment algorithms: MUSCLE, MAFFT, or ClustalW. JalView can also make pairwise alignments of user-selected sequences, build UPGMA and NJ trees based on percent identity distances, cluster sequences based on principal component analysis (PCA), and perform secondary structure prediction (4).

Geneious

Geneious is a software package recently developed by the bioinformatics company Biomatters. The fully featured pro version is commercially available, but a limited academic version is freely available for download (http://www.geneious.com). The free version of Geneious offers some visualization and analysis tools for sequences or alignments, including an interface where one can integrate sequences, alignments, 3D structures, and tree data. The editing tools, however, are only available in the pro version. The software connects to public databases for retrieval of datasets and performance of BLAST searches. Geneious is therefore an excellent tool to manage large amounts of data.

Additional analysis tools have been implemented: multiple and pairwise sequence alignment, phylogenetic tree building, dot plots, consensus sequences, and statistics of residue frequencies, pairwise similarity, etc. Furthermore, Geneious allows the user to install custom-designed plug-ins, like a PhyML plug-in for fast maximum likelihood phylogenetic reconstruction (18), a MrBayes plug-in for Bayesian phylogenetic inference (55), and a plug-in for calculating Shannon Entropy Scores (8).

GDE

GDE (Genetic Data Environment) is a user-friendly interface that integrates different bioinformatics tools, without the need to convert between different input/output file formats every time a new tool is used. GDE is very useful for the analysis of HIV, as all of the sequence-specific databases, phylogenetic datasets, and programs needed to study its diversity and molecular phylogeny can be integrated into this interface. Some of the external tools included in GDE are BLAST and FASTA for local alignment against databases, Clustal for MSA, ReadSeq for format conversion, and Phylip for phylogenetic analyses (6).

Alignment tools specific for HIV and HIV pre-built alignments

The Los Alamos HIV Sequence Database website provides several useful web tools for the manipulation of HIV sequences. Sequence Locator can be used to find the location of HIV or SIV nucleotide or protein sequences according to the standard numbering of the HXB2 genome. Gene Cutter extracts HIV genes from nucleotide sequences, which can be pre-aligned. Gene Cutter can codon-align HIV sequences, as well as translate them to amino acids. SynchAlign is another very useful tool to profile-align two alignments, which can include the pre-built HIV alignments available from this database. Primalign and Epilign align nucleotide or protein sequences, respectively, to these same pre-built HIV alignments.

The Los Alamos HIV Database also provides many other tools for working with sequences, which are not exclusive to HIV, but can also be used for other organisms. These include Gapstreeze for removing alignment columns if they present gaps above a certain percentage, Translate for translating nucleotide sequences to amino acids and Format Converter, which accepts sequences in any format and converts them into any other format. More information can be found at the Los Alamos database website.

As mentioned before, the Los Alamos HIV Database provides pre-built alignments of HIV and SIV, of the complete genome, and of specific genomic regions (e.g. LTR, *pol*, *env*, etc) (http://www.hiv.lanl.gov/content/hiv-db/ALIGN_CURRENT/ALIGN-INDEX.html) (30).

PFAM also provides alignments of retroviral protein families, such as retroviral aspartyl protease (RVP - accession PF00077), reverse transcriptase (RVT - accession PF00078), the retroviral matrix proteins (clan Matrix), and the envelope proteins (GP120 - accession PF00516 and GP41 - accession PF00517). More information can be found at the PFAM website (http://www.sanger.ac.uk/Software/Pfam/) (13).

Publishing alignments

The process of publishing alignments also implies the use of specific software. Not all alignment editors discussed above include functions for outputting ‘pretty-view’ alignments in publishable file formats.

There are also some software packages that were developed specifically for viewing and publishing alignments. These include:

- SeqPublish (http://www.hiv.lanl.gov/content/hiv-db/SeqPublish/seqpublish.html) available online;
- Highlighter (http://www.hiv.lanl.gov/content/hiv-db/HIGHLIGHT/highlighter.html) available online;
- Alscript (http://www.compbio.dundee.ac.uk/Software/Alscript/alscript.html), available for Linux and Windows;
- BOXSHADE (http://www.ch.embnet.org/software/BOX_form.html) available online or for Mac, Windows, and Linux;
- ESPript (http://espript.ibcp.fr/ESPript/ESPript/) available online and for Linux (17);
- STRAP (http://www.charite.de/bioinf/strap/) available for Linux, MacOsX, and Windows (15);

Discussion

Sequence alignment is a necessary prerequisite for the analysis of gene and protein sequence data. These analyses can include phylogenetic inference, structural analysis, and data mining. If a sequence alignment contains errors, these errors will be propagated in subsequent analysis, with the potential to result in flawed conclusions. While local alignment methods are important for searching closely related sequences and for quality control of laboratory-generated sequences, application of global alignment methods is required before proceeding with comparative sequence analysis. Recent developments aim at alignment-free phylogenetic inference (33, 51) or may improve co-estimation of alignment, phylogeny and derived parameters. An interesting development in recent years has been "statistical alignment". This class includes multiple alignment algorithms that use a statistical method, such as hidden-Markov models implemented in a Bayesian approach (2, 36, 54) or other statistically-based methods that attempt to associate a P-value to the multiple alignment (20, 42).

Visually inspecting sequence alignments is currently required to ensure their quality before proceeding to further analyses. Especially in regions with a lot of indels, such as the envelope of HIV, alignments need to be manually edited to improve their quality. In our experience, however, manual editing usually comes down to deleting ambiguously aligned gene regions. For example, hypervariable loops in HIV envelope genes, like the one shown in Figure 1, may need to be omitted from further analysis. A simple guideline would be to delete an ambiguous alignment part in between two conserved residues, for example the hypervariable V4 loop between residues 46 (F) and 70 (T) in Figure 1a. We would like to note that 'gap-stripping', which involves the removal of all alignment columns that contain gaps, and which is a frequent practice in the analysis of viral sequences, should not be considered as a standard prerequisite for further analysis. Regions where gaps have been inserted with relatively high confidence can still be informative in further analysis. For example, in our opinion, there is no need to delete the gapped region from residue 8 to residue 11 in Figure 1. More editing may be needed for nucleotide sequence alignments, in particular to restore the reading-frame in coding sequences (Figure 1b). Many software programs are available for this purpose. We briefly discussed seven of those that are considered to be relatively user-friendly and that cover common operating systems. Unfortunately, there exists no comprehensive software that combines all the useful features of the different programs we discussed. As academic funding agencies generally under-appreciate software development, researchers may sometimes need to resort to commercial software packages that can fill the gap.

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The Epidemiology of Transmission of Drug Resistant HIV-1

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1. Introduction

The use of highly active antiretroviral therapy has dramatically reduced morbidity and mortality among patients infected with HIV-1 (1,2). But the success of antiretroviral treatment is frequently limited by the emergence of HIV drug resistance (3-5). Importantly, drug resistant viruses can be transmitted to newly infected individuals (6-8). Transmission of drug resistant HIV is a major public health concern, as it could lead to a situation in which no effective drugs are available for the treatment of HIV.

A large number of epidemiological studies have addressed the important issue of transmission of drug resistant HIV. Unfortunately, the results of different studies are difficult to compare because of substantial dissimilarities in assay methodology, definitions used to classify drug resistance, time period in which the data were collected, and the population under study. Despite these differences, some conclusions can be made about the epidemiology and the impact of transmitted drug resistance.

This review summarizes the most important findings of epidemiological studies on transmission of drug resistant HIV. This review was limited to studies published in peer-reviewed journals in the last five years (2002-2006). To allow for comparison, we only considered studies that included the proportion of patients infected with drug resistant HIV and that reported the occurrence of transmitted resistance to a particular class of antiretrovirals. (The fusion-inhibitor enfuvirtide was not considered, as the epidemiological studies did not include the gp41 region where resistance to this drug emerges). Topics that will be discussed include the proportion of transmission of resistant strains in different parts of the world, trends over time, risk factors for acquiring drug resistant HIV, and the impact of transmitted resistance on future therapy. Special emphasis will be given to the methodological dissimilarities between the studies and the potential impact of these factors on the reported proportions of transmission of drug resistant HIV.

2. Methodological differences between epidemiological studies

2.1 Sampling strategy

A significant cause of dissimilarity among studies is whether the individuals sampled had a recent infection, were antiretroviral naïve, or were newly diagnosed patients (Table 1a).

Sampling limited to recently infected patients

Limiting the inclusion to recently infected patients has a substantial epidemiological benefit. Epidemiology defines the occurrence of disease as incident (new cases of disease during a specified period of time) or prevalent (number of diseased individuals at a particular point in time) (9). Incident patients acquired the virus recently, whereas antiretroviral naïve individuals who are chronically infected are defined as prevalent. In recently infected patients, the moment of infection can be estimated. Conversely, prevalent patients are a heterogeneous mixture of individuals who were recently infected and those who acquired the virus many years before but who did not yet receive treatment.

Tables 2a and 2b show an overview of, respectively, studies that limited the sampling to patients who recently acquired HIV (Table 2a) or studies that included antiretroviral naïve patients (Table 2b). The latter group consists of both recently and chronically infected individuals. A first remarkable observation is that the studies among recently infected individuals (Table 2a) used differential inclusion criteria as evidence for seroconversion in the recent past, ranging from 6 to 36 months. But of greater importance is the substantial dissimilarity in risk group distribution between studies including either

Table 1a Methodological differences in sampling strategies used in epidemiological studies

Sampling strategy	Strengths	Weaknesses
Recently infected patients	• Potential reversion is limited. • Duration of infection can be estimated. • Trends over time can be established.	• Recently infected patients are difficult to identify. • Some risk groups could be overrepresented, which limits the generalizibility of the results.
Antiretroviral naïve patients	• The largest possible number of patients can be identified. • Comparison between recently and chronically infected patients can be made. • Patients reflect clinical practice, as they are under consideration for therapy.	• Patients are more heterogeneous, as they are a mixture of individuals recently infected and those who acquired the virus many years before but who did not yet receive treatment.
Newly diagnosed patients	• Large number of patients can be identified. • Frequently the earliest sample that is available is drawn at the time of diagnosis. Compared to antiretroviral naïve patients, reversion is therefore minimized. • Local strategies can be made that allow the identification of a sample representative for the risk group distribution and geographical distribution in a particular country by using surveillance systems already in place in many countries. • Comparison between recently and chronically infected patients can be made.	• Representative sampling could depend on quality of national surveillance system. • Patients may have previously been diagnosed elsewhere.

Table 1b Methodological differences in resistance testing technologies used in epidemiological studies

Technology of testing	Strengths	Weaknesses
Genotypic assays	• Most frequently used method for classifying resistance. • Application of genotypic assays to clinical practice has shown to be beneficial in randomized clinical trials. • Less expensive and quicker. • Gives insight into evolution of resistance by detection of revertants.	• Population sequencing does not detect minor virus populations. • No consensus about amino acid substitutions that should be used to classify genotypic resistance. • Validation for particular subtypes could be limited.
Phenotypic assays	• Results are easier to interpret.	• Minor virus populations are not detected. • No consensus about fold changes in IC_{50} that are relevant for resistance to particular drugs. • More expensive and time consuming.

Table 2a Summary of studies using genotypic assays to define drug resistance among recently infected patients

Ref.	Region	Method[a]	Years of sampling	Duration infection (months)	Nr[b]	HIV risk factor (%)[c]			Incident (%)[d]					Risk factor
						MSM	IDU	HSX	any	NRTI	NNRTI	PI	MDR	
	Europe													
(61)	Europe, Canada	IAS (53)	1987–2003	<36 m	438	75	10	12	10.2	6.4	3.2	2.3	1.1	
(62)	Amsterdam, Netherlands	IAS (48)	1994–2002	<18 m	100	61	27	3	13.0	10.0	2.0	1.0	0	
(63)	France	French guidelines (64)	1996–1999	<6 m	204	60	3	34	8.8	7.4	1.0	3.9	0.5	Originating from Europe
(65)	Spain	IAS (38)	1997–2002	< 12 m	198	70	20	10	12.1	9.6	4.0	2.0	3.5	
(66)	France	IAS (47)	1999–2000	<6 m	249	57	2	32	10.4	7.6	4.0	5.6	4.8	
(67)	London, UK	IAS (38)	2000–2004	<6 m	140	91		9	6.4	2.1	4.3	1.4	1.4	
(68)	France	IAS (51)	2001–2002	<6 m	301	58	0	32	14.0	10.3	3.3	4.3	0.6	
	North America													
(57)	North America	IAS (50)	1995–2000	<12 m	301		23		12.3	10.9	3.5	3.3	5.7	
(69)	New York, USA	IAS (38)	1995–2004	<12 m	361	97[e]			18.8	13.0	8.0	5.0	5.8	
(58)	San Francisco, USA	IAS (46)	1996–2001	<12 m	225	86			23.1	16.0	8.0	5.8	6.2	
	Africa													
(70)	Abidjan, Côte d'Ivoire	Not reported	1997–2000	<36 m	99				0	0	0	0	0	
	South-America													
(71)	Argentina	IAS (38)	2004–2005	<9 m	52	45	2	52	7.7	1.9	5.8	0	0	

[a] Definition used for classifying HIV drug resistance. "IAS" means that the mutation-list defined by the IAS was used; the version of the list is given by the reference.

[b] Nr=number of patients included.

[c] The HIV risk factors were classified as MSM (men-having-sex-with-men), IDU (Intravenous Drug Users) and HSX (Heterosexual).

[d] Resistance was subdivided into particular classes of antiretrovirals. The column "Any" is the proportion of patients infected with a virus that contained at least one resistance-associated mutation. "MDR" is multi-drug-resistance or resistance to at least two classes of antiretrovirals.

[e] data from 2003–4 only.

Table 2b Summary of studies using genotypic assays to define drug resistance among antiretroviral naïve patients

Ref.	Region	Method[a]	Years of sampling	Nr[b]	HIV risk factor (%)[c]			Prevalent (%)[d]					Risk factor
					MSM	IDU	HSX	any	NRTI	NNRTI	PI	MDR	
	Africa												
(59)	Abidjan, Côte d'Ivoire	IAS (49)	unreported	20				0	0	0	0	0	
(60)	Nigeria	Not reported	unreported	18				0	0	0	0	0	
(88)	Yaounde, Cameroon	IAS, version not reported	2001–2002	102				7.8	2.9	2.0	2.9	0	
(89)	Lusaka, Zambia	IAS (49)	2000	28				0	0	0	0	0	
(90)	Abidjan, Côte d'Ivoire	IAS, version not reported	2001–2002	107	0	0	100	5.6	0.9	3.7	0.9	0	
(91)	DR Congo	Stanford HIV database	2002	70				4.3	0	1.4	2.9	0	
(88)	Ouagadougou/Bobo Dioulasso, Burkina Faso	IAS, version not reported	2003	97				8.3	2.1	4.1	2.1	0	
(92)	Nkwen/Kumbo, Cameroon[e]	IAS (38)	2004	54				13.0	3.7	5.6	7.4	3.7	
	Europe - West												
(17)	Europe, Israel	IAS (47)	1996–2002	2208	43	15	41	10.4	7.5	2.9	2.5	2.0	Infection <12 m, subtype B
(77)	United Kingdom	Stanford HIVdb algorithm	1996–2003	2357	63	17	2	14.2	9.9	4.5	4.6	3.3	Recent infection, ethnic group
(78)	Israel	IAS (51)	1999–2003	176	10	23	58	14.8	2.8	8.5	5.1	0.6	Infection in Israel
(79)	Sweden	IAS (50)	1998–2001	100	40	2	41	9.0	5.0	3.0	1.0	0	
(80)	Denmark	Not reported	2000	96				2.1	2.1	0	0	0	
(26)	Nordrhein-Westfalen, Germany	IAS (52)	2001–2003	269	48			11.2	8.6	4.1	1.5	1.5	subtype B virus, white ethnicity, shorter duration of infection
(81)	Galicia, Spain	Stanford HIV database	2000–2002	85	18	32	47	7.1	5.9	0	1.2	0	
(82)	London, UK	IAS (50)	1999–2001	72	0	0	100	6.9	1.4	2.8	4.2	2.8	
(83)	Greece	IAS (53)	2002–2003	101	55	3	23	8.9	5.0	4.0	0	0	
(68)	France	IAS (51)	2001–2002	363	31	8	51	9.1	7.2	1.7	1.9	1.7	
	Europe - East												
(94)	Former Soviet-Union	Stanford HIV database	1997–2004	278	3	84	12	16.6	5.4	7.6	4.0		
(93)	Tbilisi, Georgia	Stanford HIV database	1998/2003	48	2	65	27	4.2	4.2	0	0	0	
	Latin-America												
(95)	Porto Alegre, Brazil	Stanford HIV database	unreported	108				2.8	0.9	1.9	0	0	
(96)	Rio de Janeiro, Brazil	IAS (50)	1998	47				8.5	8.5	0	0	0	

Table 2b cont.

Ref.	Region	Method[a]	Years of sampling	Nr[b]	HIV risk factor (%)[c]			Prevalent (%)[d]					Risk factor
					MSM	IDU	HSX	any	NRTI	NNRTI	PI	MDR	
(97)	Brazil, Sao Paolo[f]	IAS (38)	1998–2002	341				6.2	3.5	0.9	1.2	0.6	Recent infection, non-B subtype
(98)	Brazil	IAS (50)	2001	339	27	5	62	6.5	2.1	2.4	2.4	0.3	
(99)	Peru	IAS (51)	2002–2003	359	100	0	0	3.3	2.2	0.8	2.0	1.7	
	North America												
(72)	USA	IAS (47)	1997–2001	1082	45	10	45	8.3	6.4	1.7	1.9	1.3	Caucasian, partner taking HIV medication, MSM>IDU>HSX
(73)	Boston, USA	IAS (50)	1999	88	20	31	51	18.2	13.6	4.6	3.4	2.3	
(74)	USA	IAS (51)	1999–2001	491	56	15		10.8	7.7	3.1	0.6	0.6	Non-Hispanic white,40% increase in risk for acquiring resistant virus per year
(75)	Canada	IAS (48)	2000–2001	715	26	33	17	8.1	4.1	1.4	1.5	1.0	Infection <6 m, lower among African or Caribbean ethnicity
(76)	San Francisco, USA	IAS (33)	2004	118				14.4	6.8	9.3	2.5	2.5	
	Asia												
(100)	Ho Chi Minh City, Vietnam	IAS, version not reported	2001–2002	200		43		6.5	4.5	0	2.0	0	
(101)	Kuala Lumpur, Malaysia	IAS (38)	2003–2004	100			57	1.0	0	1.0	0	0	

[a] Definition used for classifying HIV drug resistance. "IAS" means that the mutation-list defined by the IAS was used; the version of the list is given by the reference.

[b] Nr=number of patients included.

[c] The HIV risk factors were classified as MSM (men-having-sex-with-men), IDU (Intravenous Drug Users) and HSX (Heterosexual).

[d] Resistance was subdivided into particular classes of antiretrovirals. The column "Any" is the proportion of patients infected with a virus that contained at least one resistance-associated mutation. "MDR" is multi-drug-resistance or resistance to at least two classes of antiretrovirals.

[e] Study used proviral DNA.

[f] Study only included blood-donors.

recently or chronically infected patients. Men-having-sex-with-men (MSM) were the predominant risk group (proportion ranging between 57% and 92%) in studies of recently infected patients in Western Europe or North America (Table 2a). In the same geographical regions, MSM was also a common risk group among prevalent antiretroviral naïve patients (Table 2b). But the proportion of MSM had percentages ranging between 18% and 63%, substantially lower than in most studies of recently infected patients. An important explanation for this dissimilarity in risk group distributions between the studies in Tables 2a and 2b is that, in some European countries, patients who acquired HIV through heterosexual contact are more likely to come from regions with a history of limited access to antiretroviral drugs (10-12); amongst them, transmission of resistance will be rare. In addition, most of these patients are expected to have been infected before arrival in Europe and are therefore expected to be underrepresented among recently infected patients. Finally, it has been reported that MSM more frequently take an HIV test (13). As a consequence, they are likely to be identified earlier during the course of their infection. Therefore, studies limited to recently infected patients may not be representative of all HIV-infected patients and are likely to overestimate the true size of the problem of transmitted drug resistance.

Limiting the inclusion to recently infected individuals also has an advantage from a virological point of view, as reversion of transmitted drug resistance will be minimized. Reversion can occur because mutations conferring resistance to antiretroviral drugs commonly - but not always - result in a virus that replicates less efficiently than wild-type HIV (14,15). Thus, the drug resistant virus could be outgrown by faster-replicating revertant viruses. In addition, reversion could result in a viral sequence intermediate between the wild type and a resistance associated substitution. An important example of this phenomenon occurs at codon 215 of reverse transcriptase. Here, the resistance associated substitutions T215F and T215Y require two nucleotide mutations for reversion to wild type. But in isolates obtained from patients who had not receive antiretroviral treatment for their HIV-infection, unusual codons are frequently found that are intermediates between wild type and T215F/Y (16-19). Interestingly, viruses with a reversion at codon 215 have a decreased genetic barrier for the selection of the resistance-associated amino acid substitution T215Y (19).

Intermediates have not been reported for most other codons where resistance associated substitutions can emerge. As a consequence, reversion is expected to frequently result in a susceptible wild-type virus. In this context, it is important to note that drug resistant HIV can persist for decades by establishing a latent infection in resting memory CD4-positive cells, and perhaps other cells (15). Hence, inclusion of chronically infected antiretroviral naïve patients could underestimate the size of the problem, as resistance - still present as a latent infection - may no longer be detected due to reversion to the wild-type sequence in viral RNA isolated from plasma. Several studies have shown a remarkable persistence of particular patterns of transmitted drug resistance in plasma over time (20-23), indicating that reversion of some mutational patterns only occurs to a limited extent. In addition, a recent study (24) proposed compensatory fixation as a possible explanation for the in vivo persistence of some mutational patterns. The study reported the prolonged persistence (up to 4 years) of viruses with multiple protease mutations after treatment with protease inhibitors was stopped (treatment with RT inhibitors was continued). It was found that these viruses have partially compensated for the initial loss in replication capacity. Reversion of a single mutation therefore causes a further reduction in replication capacity and, as a consequence, the route to wild type is blocked (24). A similar phenomenon was observed in transmitted resistance (25).

Sampling extended to antiretroviral naïve and/or newly diagnosed patients

Patients recently infected with HIV are difficult to identify. But, because of the limited extent to which reversion occurs, epidemiological studies could also include patients living with HIV for a longer period of time who have not received treatment at the time they were sampled; these chronically infected antiretroviral naïve patients are easier to identify. Hence, studies also including antiretroviral naïve patients could identify a larger number of individuals during a shorter period of sampling. This is nicely illustrated by comparing the number of patients included in the studies summarized in Tables 2a and 2b; all studies with more than 500 patients also included antiretroviral naïve individuals.

But antiretroviral naïve patients can be sampled using several strategies. For instance, patients who had not been treated with antiretrovirals at the time of inclusion can be sampled (17). In addition,

a resistance test can be done on a sample collected just before treatment is initiated (26). Sampling is preferably limited to newly diagnosed patients, as this approach allows a resistance test to be performed on the earliest available sample, thus minimizing reversion (27). In addition, a substantial number of countries have HIV surveillance systems that are limited to newly diagnosed patients (10-12,28,29). Using these surveillance systems, local sampling strategies can be made that allow for the identification and inclusion of individuals who are representative of the risk group distribution and geographical distribution of local HIV epidemics. Finally, newly diagnosed patients also include individuals who recently acquired HIV.

2.2 Assay methodology and definitions used to classify resistance

Genotypic assays

Both genotypic and phenotypic assays are used for resistance testing, and the strengths and weaknesses of each methodology are summarized in Table 1b. The majority of epidemiological studies have used genotypic testing (Tables 2a and 2b). Genotypic assays identify the mutations that cause amino acid substitutions associated with drug resistance (30). Importantly, most studies have used population sequencing, which fails to detect and quantify minorities of drug-resistant quasi-species below 25% (31). Using methodology that allows the quantification of minor viral populations has demonstrated that conventional population sequencing considerably underestimates the size of the problem of transmitted resistance (31,32).

Studies using genotypic assays define resistance as the presence of one or more amino acid substitutions included in the resistance guidelines published by the International AIDS Society of the United States (IAS-USA) (Tables 2a and 2b). This is an important advantage, as it facilitates the comparison of rates found between studies. But unfortunately, the IAS-USA resistance guidelines are not designed for this purpose. Indeed, the experts who wrote the guidelines indicate that the list should be used cautiously in studies of the transmission of resistance (33).

Several problems could arise when applying the IAS-USA resistance guidelines in epidemiological studies on transmission of resistance. For instance, the guidelines include polymorphic substitutions that occur naturally in HIV-1 sequences obtained from individuals without any previous drug exposure (34-36). Inclusion of these polymorphic substitutions could overestimate the size of the problem. In this respect, it is also important to discuss the distinction the IAS list makes between major and minor protease substitutions. According to the definition provided in the IAS list, major substitutions by themselves reduce drug susceptibility. Minor substitutions improve, in some cases, the replicative capacity of HIV carrying major substitutions (37), but do not by themselves have a significant effect on drug susceptibility (37,38). Most minor protease substitutions are polymorphic, as they are also common in sequences from patients who have not been exposed to antiretrovirals (36,39). Due to the polymorphic nature of most minor substitutions, studies only consider the major ones as evidence of transmission of drug resistance.

Furthermore, the IAS list may not include all relevant substitutions, as the guidelines are based on published data. Current published data rely mainly on isolates obtained from persons treated for a limited period of time with a single inhibitor. Today, therapeutic regimens are increasingly complex, and a large number of novel resistance-associated substitutions have emerged that are not currently included in the IAS list (35,36,40).

The amino acid substitutions included in the IAS-USA resistance guidelines have mostly been identified in sequences of subtype B. Interestingly, particular subtypes have different mutational patterns (41). But codons at positions with major protease and reverse transcriptase drug resistance-associated substitutions are generally well-conserved across the subtypes (42). Nonetheless, some important differences in resistance pathways are found in subtype B and non-B strains. For instance, in patients failing nelfinavir, subtype B strains most frequently develop the D30N amino acid substitution, whereas other subtypes more commonly develop L90M (43,44). Similarly, upon failure to efavirenz, V106M is more frequently observed in subtype C as compared to B (45).

Finally, the IAS list is regularly updated to include novel substitutions that have been identified as relevant for drug resistance (33,38,46-53). But these updates complicate the comparison between stud-

ies performed at different periods in time. In addition, the IAS list does not consistently list the same mutations. For instance, the RT amino acid substitution V118I was included in previous versions of the IAS list (48,52,53), but was omitted from the most recent update of the list (54). Importantly, the V118I substitution is found in 2-3% of subtype B sequences obtained from patients who did not take antiretroviral drugs (55). Hence, inclusion of V118I overestimates the size of the problem of transmitted resistance. Similarly, the protease V32I substitution was classified in previous versions as a minor mutation (48,52,53), but the most recent update of the list classifies this mutation as major (54).

To facilitate any comparison between studies, the methods section of reports on the epidemiology of transmission of drug resistant HIV should include the mutations considered. In addition, the frequency of the most commonly found amino acid substitutions should be listed in the results section.

Phenotypic assays

A small number of studies classified resistance using phenotypic assays (Table 3). All of these studies also defined drug resistance by means of a genotypic assay (and thus are also included in Tables 2a and 2b). A phenotypic assay measures the in vitro susceptibility of HIV to antiretrovirals. For this purpose, a recombinant virus including the protease and RT gene from the patient's plasma is created. Susceptibility to particular antiretrovirals is then calculated as the fold change in drug concentration at which 50% (IC_{50}) of replication is suppressed, as measured by comparing the IC_{50} values of a reference strain and the recombinant virus (16,56).

Unfortunately, the cut-offs used in phenotypic assays for defining drug resistance are not clearly described. All studies defined phenotypic resistance using cut-offs in IC_{50} at 2.5 and 10 fold (57-60). But the cut-offs above which there is detectable impairment in virological response is known to vary by drug. Surprisingly, only one study used various cut-offs for different antiretrovirals based on assay precision, biological variability, and limited clinical experience (58).

Using different cut-offs had a substantial impact on the proportion of patients in whom transmitted resistance was detected (Table 3). All studies reported a prevalence of at least 10% when using a cut-off of 2.5. Conversely, the size of the problem of resistance was limited if only a fold change in IC_{50} above 10 was considered. Importantly, in all studies, the reported prevalence based on phenotypic assays deviated substantially from the result obtained using genotypic resistance (Figure 1).

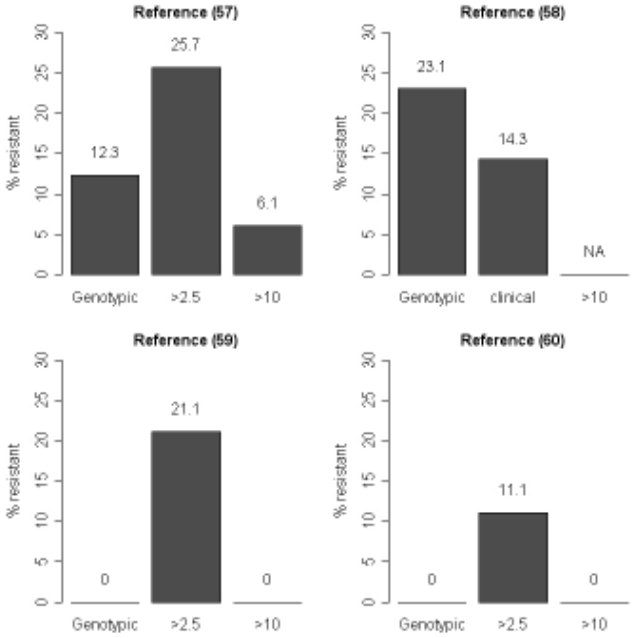

Figure 1. Comparison of genotypic and phenotypic resistance tests. The bars labeled 'genotypic' represent the proportion of patients infected with a drug resistant virus according to the results of genotypic assays. Similarly, the bars >2.5 and >10 represent the proportion of transmitted phenotypic resistance using a fold-change in IC50 of, respectively, at least 2.5 or 10. The study by Grant et al. (reference 58) did not include the fold changes above 2.5, but used clinical cut-offs that varied for each drug.

Table 3 Summary of studies using phenotypic assays to define drug resistance

Ref.	Region	Method	Years of sampling	Nr[a]	IC_{50} fold change Cut-off	Proportion resistant (%)[b] Any	NRTI	NNRTI	PI	MDR
	North America									
(57)	North America	PhenoSense HIV, ViroLogic	1995–2000	377	>2.5	25.7				
					2.5–10	19.6				
					>10	6.1	3.4	3.4	2.7	2.7
(58)	San Francisco, USA	PhenoSense HIV, ViroLogic	1996–2001	210	Clinical cut-offs[c]	14.3	7.6	5.7	3.8	2.4
					>2.5		7.1	24.8	11.9	
					>10		3.3	5.7	2.9	
	Africa									
(59)	Abidjan, Côte d'Ivoire	Antivirogram, Virco	unreported	19	>2.5[d]	21.1	5.3	10.5	15.8	0
					>10	0	0	0	0	0
(60)	Nigeria	PhenoSense HIV, ViroLogic	unreported	18	>2.5	11.1	0	0	11.1	0
					>10	0	0	0	0	0

[a] Nr=number of patients included.

[b] Resistance was subdivided to particular classes of antiretrovirals. The column "Any" is the proportion of patients infected with a virus resistant to at least one antiretroviral drug. "MDR" is multi-drug-resistance or resistance to at least two classes of antiretrovirals.

[c] The clinical cut-offs in IC_{50}-fold change varied per antiretroviral drugs. For the NRTIs these cut-offs ranged between 1.7 (stavudine, didanosine and zalcitabine) and 4.5 (lamivudine, zidovudine and abacavir). The clinical cut-offs for all NNRTIs and PIs were respectively, at least 10 and 4 or greater.

[d] The article mentioned low-level resistance.

3. Summary of the reported results

3.1 Epidemiology of transmitted resistance

Recently infected patients

Studies limited to recently infected patients were predominantly performed in Europe and North America (Table 2a). Interestingly, the incidence figures reported in Europe (ranging between 6.4% and 14.0%) (61-68) were generally lower than those in North America (12.3% to 23.1%) (57,58,69). The magnitude of multi-class resistance, defined as evidence of decreased susceptibility to at least two different classes of antiretrovirals, was also substantially higher in North America (about 6%) as compared to Europe (generally <2%). This indicates that the problem of transmitted resistance is more complex in North America. Furthermore, in both of these parts of the world, resistance was most frequently found for NRTIs (nucleoside reverse transcriptase inhibitors).

The single African study, which only included recently infected individuals, found no evidence of transmitted drug resistance (70). The absence of resistance among these patients most likely reflects the limited availability of antiretrovirals in Africa.

A remarkable study from Argentina reported an incidence of 7.7% (71). The results of this study are interesting because the Argentinean ministry of health has sponsored a policy of universal access to antiretroviral drugs since 1990. It is therefore important to note that the figure reported in this South American country was lower than most estimates from Europe and North America. Genotypic resistance was primarily found for NNRTIs (non-nucleoside reverse transcriptase inhibitors). In addition, transmitted multi-class resistance was not reported.

Antiretroviral naïve and newly diagnosed patients

A considerable number of studies have reported on the epidemiology of transmitted drug resistant HIV among prevalent patients who had not received antiretroviral therapy at the time they were sampled (Table 2b). These studies included antiretroviral naïve patients on almost all continents. Importantly, evidence of transmitted resistance has been observed all over the world. But a consistent finding among antiretroviral naïve patients, irrespective of where they were sampled, is that the prevalence of multi-class resistance is limited.

Studies from North America (72-76) and Western Europe (17,26,68,77-83) generally reported the highest prevalence estimates of transmitted drug resistant HIV (8-18% and 2-14%, respectively). This could be ascribed to the earlier period in time when patients were sampled in these regions. In addition, it could be due to the widespread availability of antiretroviral drugs for a substantial period of time in industrialized countries. A notable exception to the higher prevalence of transmitted resistance in North America and Western Europe is Denmark. A study from this country found evidence of transmitted resistance in only 2.1% of the included individuals (80).

An interesting observation that can be made from the results in Table 2b is that transmitted resistance in North America and Western Europe was most frequently found for NRTIs, irrespective of the years in which patients were sampled. It should be noted that one study from San Francisco (76) was an exception, reporting that transmitted NNRTI resistance was the most common. In other parts of the world, transmitted resistance was generally more homogenously distributed across the various antiretroviral drug classes. A possible explanation for this dissimilarity is that in Western Europe, the USA, and Canada, antiretrovirals were introduced well before HAART (highly active antiretroviral treatment, or the combination of the at least two different classes of anti-HIV drugs) became available in 1996. Before then, treatment of HIV consisted of a single NRTI, usually zidovudine or lamivudine. Resistance to mono-therapy with these drugs emerges rapidly (84-86) and it is thus very likely that a large number of NRTI-resistant viruses circulated at that time. Indeed, the first published case reports in the early 1990s described transmitted zidovudine resistance (6-8). HAART successfully suppresses viral replication making the emergence of resistance less likely. Therefore, in countries where treatment started at the time when HAART had become available, less drug resistant viruses are expected to circulate. This hypothesis is also supported by the observation that rates of transmitted NRTI resistance

were generally highest in Europe and North America (87).

Studies performed in Africa were usually small, with sample sizes ranging between 18 and 107 patients. As could be expected based on the small scale on which antiretrovirals are available in Africa, transmission of drug resistance did not occur frequently, with estimates between 0 and 13.0%. Similarly, the mutational patterns were not complex, as resistance was always observed for only one class of antiretrovirals (59,60,88-92). Nonetheless, one study from Cameroon reported a considerable prevalence of transmitted resistance of 13.0%. But this study used a dissimilar method, as the genotyping was done using proviral DNA. In addition, the researchers analyzed at least four clones per sample. Interestingly, the researchers reported that the drug resistance-associated substitutions were, in all but one case, present as minor populations, as evidence of resistance was only observed in only one of the four clones (92). But these minor viral variants cannot be detected by the population sequencing used in other studies (31). Excluding the drug resistant mutants found as minor populations from the analysis resulted in a decrease of the prevalence of transmitted resistance from 13.0% (7/54) to 1.9% (1/54) (92).

Of particular interest were the two reports from the former Soviet Union (93,94). Since the mid-1990s, this part of the world has experienced a progressively growing epidemic, mostly limited to intravenous drug users. Importantly, Eastern Europe is the region of the world with the fastest growing HIV epidemic (29). One report, from the republic of Georgia, predominantly included intravenous drug users and found a limited prevalence of transmitted resistance of only 4% (93). The other report from Eastern Europe included patients from across the former Soviet Union (94). Surprisingly, the study found a prevalence of 17%, which is among the highest reported anywhere in the world.

In Latin America most reports that limited the inclusion to antiretroviral naïve patients came from Brazil (95-98). This country provides important information, as the Brazilian ministry of health has been sponsoring a policy of universal access to antiretroviral drugs since 1996 (98). The prevalence of transmitted resistance has had values ranging between 2.8 and 8.5% (95-98), generally lower than most reports from Europe and North America. Transmitted multi-class resistance in Brazil was only observed in a very limited fraction (at most 0.6%) of antiretroviral naïve individuals (95-98). Similarly, a study among MSM in Peru found a low prevalence of transmitted resistance of only 3.3% (99).

Two reports from Asia found that the size of the problem of transmitted resistance was limited (100,101). A study from Vietnam found a prevalence of 6.5% among 200 antiretroviral naïve individuals (100). Similarly, a Malaysian study reported evidence of transmitted resistance in only one individual among 100 antiretroviral naïve patients (101).

Comparison of recent vs. chronic infection

A small number of studies that sampled antiretroviral naïve patients also compared the proportion of resistance between recently and chronically infected individuals (Table 4) (17,72,75,83,97,99). All but one of these studies (17,72,75,83,97) found that transmission of drug resistance was most frequent among patients who recently acquired HIV. But two reports found a decreased risk for transmitted resistance among recently infected patients as compared to chronically infected individuals (76,99).

Table 4 Comparison of proportion of transmitted resistance among recently and chronically infected patients

Ref.	Region	Years of sampling	Classification of recent infection	Number of patients		Proportion resistant (%)	
				Recent	Chronic	Recent	Chronic
(17)	Europe, Israel	1996-2002	<12 m	777	607	13.5	8.7
(72)	USA, 10 cities	1997-2001	<6 m	182	767	11.5	7.4
(75)	Canada	2000-2001	<6 m	221	494	12.2	6.3
(76)	San Francisco, USA	2004	Detuned assay (118,119)	42	76	9.5	14.5
(83)	Greece	2002-2003	<12 m	18	79	22.2	6.3
(97)	Sao Paolo, Brazil	1998-2002	Detuned assay (120)	55	280	12.7	5.0
(99)	Peru	2002-2003	Detuned assay (121)	33	326	3.0	3.4

The epidemiological dissimilarity in transmitted resistance between recently and chronically infected patients is due to a complex interplay of various factors. First, the discrepancy is partially explained by the limited degree to which reversion occurs (20,22). In this context, it should be noted that revertants at codon 215 are classified as transmitted resistance. Furthermore, patients who are identified earlier during the course of their HIV-infection generally have a different risk-group distribution. As a consequence, the dissimilarity could be due to the higher prevalence of transmitted resistance in particular risk groups that are more common among patients identified earlier after seroconversion. Finally, both study groups were infected at different moments in time. The lower prevalence among chronically infected patients could therefore reflect a lower prevalence of transmitted resistance in the past.

3.2 Time trends

In this report, the comparison of transmitted resistance over time was limited to patients who were newly infected. Only these patients were considered, as transmission of resistance among chronically infected patients also reflects the risk for acquiring a resistant virus many years ago.

The results from studies that looked at trends are inconsistent, with some studies finding either a substantial increase (57,61,69) or decrease (62,65,67) over time. In addition, other studies reported a slight decrease in transmitted resistance followed by a second peak (17,58,72). The inconsistent findings could be explained by local differences. But the comparison between time periods is complicated, as many studies reported that the population under study also changed over time (61,62). Also, there was a considerable dissimilarity between studies regarding the particular time periods that were compared.

New insights in the treatment of HIV and novel drugs have been developed during the last decade (102-105). As a consequence, it can be expected that treatment has improved over time, and this could have an impact on transmitted resistance. But based on the reports published in recent years, it is not yet possible to conclude whether changes in treatment had a beneficial or detrimental impact on the size of the problem of transmitted resistance over time.

3.3 Risk factors for acquiring drug resistant HIV

Several studies have reported on the risk factors for acquiring a drug resistant virus. Importantly, studies from North America and Europe reporting on risk factors found that transmission of resistance most frequently occurred among Caucasians, as compared to other ethnic groups (26,72,74,75). This dissimilarity is most likely caused by the fact that antiretrovirals have been available for a prolonged period of time in North America and Europe, but have been less accessible in other parts of the world. As non-Caucasians are more likely to carry viruses originating from recent immigrants, they are thus less likely to carry a drug resistant virus.

An interesting observation was that viruses in which drug resistance-associated substitutions were identified were predominantly of subtype B (17,26). HIV-1 subtypes have a distinct geographical distribution, with subtype B predominating the epidemic in North America and Western Europe. Clade B accounts for only a minority of infections in Africa, where subtypes A and C predominate, and a number of other clades are also circulating at a high level (106-108). Subtype B viruses thus predominantly circulate in areas where antiretrovirals are readily available. This explains the higher prevalence of transmitted resistance among subtype B.

In summary, the comparison of reported risk factors suggests that transmission of resistance is most likely in patients originating from areas where antiretrovirals are available on a large scale. As a consequence, immigration from areas with limited access to antiretrovirals could have a profound impact on transmitted resistance.

3.4 Impact of transmitted resistance on treatment efficacy

When treatment of patients who have failed antiretroviral therapy is guided by expert interpretation of genotypic resistance, significantly improved virological outcome is achieved (109-111). These results cannot easily be extrapolated to transmitted resistance, as mutational patterns are more complex among patients failing antiretroviral treatment. For instance, contrary to transmitted resistance, HIV

multi-class resistance is very common in individuals who fail treatment (3-5).

Several of the epidemiological studies discussed in this review analyzed the impact of transmitted resistance on initial antiretroviral treatment. Studies that did not use genotypic information in the initiation of treatment found that antiretroviral naïve patients infected with a drug resistant virus took a longer time to reach viral suppression after starting treatment (57,58,63). In addition, among patients who had a relapse of viremia after viral suppression, the length of time to virologic failure was shorter among individuals with transmitted resistance (57). Complete viral suppression was generally achieved in the vast majority of patients, irrespective of baseline susceptibility patterns (57,58). Nonetheless, the longer time needed to achieve complete viral suppression may permit sufficient further rounds of viral replication to select for additional drug-resistant variants (112), which could be detrimental during a later stage of treatment.

Conversely, studies in which treatment was optimized based on interpretation of resistance found that the time to virological suppression was similar irrespective of baseline susceptibility (26,67,69,109-111). Therefore, guidelines (27,105) recommend resistance testing before initiation of treatment in areas where the prevalence of transmitted resistance is unknown or greater than 5% (105) or 10% (27).

4. Conclusions and summary

The incidence and prevalence of transmitted resistance show substantial variability among studies. The dissimilarities among studies are to some extent ascribed to whether recently or chronically infected patients were sampled. Limiting the inclusion to recently infected patients has some important virological advantages (*i.e.*, potential reversion minimized) and epidemiological advantages (*i.e.*, duration of infection can be estimated), but particular routes of transmission seem to be over-represented. The latter is most likely due to differences in HIV testing behavior between risk groups. As a consequence, studies limited to patients that recently acquired the virus may not be representative of all HIV infections in a particular geographic region. Fortunately, transmitted drug resistant HIV persists for a considerable period. This key observation implies that epidemiological studies on transmitted resistance could also include chronically infected patients who had not received antiretroviral treatment. Notably, most patients are identified when they have entered the asymptomatic phase of AIDS.

As an example of progress in surmounting the problem of differences in study methodologies, we would like to mention the SPREAD program, which is now being implemented by the EuropeHIVResistance Network. This program has investigated transmission of resistance and its determinants across Europe. For practical reasons, the study group consisted of newly diagnosed patients. Sampling newly diagnosed individuals allowed us to obtain the earliest available sample. Importantly, patients were sampled according to a uniform strategy that enabled the identification of those who were representative for the risk group distribution and geographical distribution of the HIV epidemic in each country. Using this strategy, we identified 1083 patients from 17 European countries. A considerable proportion (22%) of the patients had laboratory evidence of recent seroconversion (<1 year) (113). We expect that the results of this large-scale systematic study will shed new light on the transmission of drug resistance in Europe.

The most important risk factor for transmitted resistance seems to be the large-scale availability of antiretrovirals in the area where infection occurred. Immigration from areas with limited or no access to antiretrovirals could therefore have a profound impact on the size of the problem of transmitted resistance (*e.g.*, immigration from Africa to Europe). In theory, the occurrence of transmitted resistance in a risk group sampled in a particular geographical region could increase but, due to immigration, the prevalence could decrease in the population of antiretroviral naïve individuals living in the same area. Therefore, absolute numbers and the occurrence of transmitted resistance should be provided for every risk group.

The vast majority of studies used population sequencing for determining genotypic resistance. This type of genotypic assay sequencing does not allow detection of minor populations present in <25% of the sequences. Virtually all studies therefore underestimate the size of the problem of transmitted resistance. Importantly, there is a surprising lack of consensus with respect to the amino acid substitu-

tions that are of relevance for transmitted drug resistance. Studies using different methods for classifying resistance based on genotypic assays are therefore difficult to compare. Thus, we recommend that the methods section of all epidemiological studies should include the particular amino acid substitutions that were analyzed. In addition, the frequency of the most commonly-found mutations should be listed in the results section.

Transmitted multi-class resistance is rare in all parts of the world. Nonetheless, epidemiological studies that followed patients after the start of antiretroviral treatment showed that therapy guided by resistance testing performed before the commencement of antiretrovirals has a beneficial impact on the length of time to reaching virological suppression. Resistance testing on the earliest available sample is therefore recommended in areas with a prevalence of transmitted resistance that exceeds 5-10%.

Current studies on transmission of drug resistance only consider three classes of antiretroviral drugs (NRTIs, NNRTIs, and protease inhibitors). But since 2003, the fusion inhibitor enfuvirtide is also available in clinical practice (114,115). Transmitted resistance to enfuvirtide does not presently seem to be a problem, as only two cases have been documented (116). A likely explanation for the very limited enfuvirtide resistance is that this drug is used by only a small number of patients. For example, a Dutch online database on drug utilization in the Netherlands reported that in 2005 only 89 patients used enfuvirtide, while almost 9,000 individuals used NRTIs, about 5,000 persons used NNRTIs, and more than 3,000 patients took protease inhibitors (117). Inclusion of enfuvirtide resistance in surveillance programs means that a genetically variable region of the envelope should be genotyped, and this procedure is not currently part of routine clinical practice. Therefore, this test only seems warranted if a substantial number of HIV patients start using this drug. Similarly, transmission of resistance to novel drugs such as CCR5 and integrase inhibitors should only be considered if large numbers of patients start using these drugs. Before large scale epidemiological studies are set up, pilot studies in particular risk groups could be performed to determine if any transmission of resistance to novel classes of drugs is found.

In summary, transmission of resistance has been reported in all parts of the world. The size of the problem varies between 0 and 25% and seems to be the highest in areas where antiretrovirals have been available for a long period of time. Antiretrovirals have shown to dramatically decrease morbidity and mortality among people living with HIV (1,2) and are therefore increasingly provided in many parts of world. Monitoring of transmitted resistance continues to be needed to allow a timely modification of antiretroviral treatment guidelines. Importantly, when comparing results from various studies, the differences in research methodology should be taken into account.

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Search Tools in the HIV Databases

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The Los Alamos National Laboratory HIV databases serve as a repository for large amounts of information about HIV. A challenge for us is to find ways to make this information as useful and as easily accessible as possible for our experimentalist colleagues. Over the years, we have developed a variety of web-based tools for searching the databases that we maintain. We hope that by providing a general overview of these search tools, this article will familiarize our website users with new ways of accessing useful data.

Below is a list of our database search programs, followed by detailed descriptions and examples of each.

ALL DATABASES

Site search Find web pages on all our websites.

SEQUENCE DATABASE

Sequence Search Interface Find, align, download, build tree, and analyze sequences.

Advanced Search Interface Generate a custom search interface for any database fields.

Geography Find and map the number of sequences of each genotype by region or country.

IMMUNOLOGY DATABASE

CTL(CD8+) and T-helper(CD4+) Search Find CTL and T-helper epitopes.

Antibody Search Find HIV-specific antibodies.

VACCINE TRIALS DATABASE

Regular Search Search for studies meeting your criteria.

Cross-Table Search Generate cross-tabulated data, based on any two database criteria.

Adjuvants/Stimulants Search a separate database of substances used as adjuvants/stimulants in vaccine trials.

RESISTANCE DATABASE

Simple Search Search for drug resistance mutations by gene, compound, drug class, and amino acid position only.

Advanced Search Search by a wider selection of fields.

ADRA Identify mutations associated with anti-HIV drug resistance in your query sequence.

I. ALL DATABASES

Site Search

The site search can be accessed from the menu bar found on most pages of the Sequence and Immunology databases, shown below. It is a Google-based search for words or phrases in any of the LANL HIV and HCV databases. For example, if you want to know what pages we have about circulating recombinants of HIV, type "CRF" or "recombinants" into the search box. The searches have the same advantages and disadvantages as all Google searches.

II. SEQUENCE DATABASE

The sequence database (www.hiv.lanl.gov/content/hiv-db) contains all HIV-1, HIV-2, SIV, and SHIV sequences that have been deposited in public databases. We have a slight lag-time in retrieving sequences, so some very recent sequence submissions may not be available at the time of search. We provide three search interfaces for extracting sequences and related information: Regular search, Advanced search, and Geography search.

Regular Search Interface

The information in the sequence database can be accessed via a versatile, user-friendly search interface that allows searches on approximately 30 different fields. An important feature is the ability to search by genomic region. For example, you can locate all sequences in the database that span the V1–V3 region of *env*. There is also an option to include sequences that are located in that region but do not cover it completely; this option is labeled "Include fragments of minimum length __". The minimum length specified is the length by which a sequence needs to overlap the region of interest in order to be included. In the example shown below, we are using the regular search interface to select sequences of subtype C from the US. We have further limited the search to only sequences from patients with >2 sequences available in the database, and to the Pol region, including fragments over 100 bp long.

Fields available on the Search Interface Mousing over the names of most fields gives a very brief description of each field; more help is available by clicking on the field name. Seven fields are always included in the output list: accession number, sequence name, subtype, sampling country, sampling year, genomic region, sequence length, and organism. All additional fields that are included in the search are also listed in the output. (Note that this can result in wide pages for some searches, such as Author names.) A complete description of all database fields is found in the search interface help file (www.hiv.lanl.gov/components/hiv-db/combined_search_s_tree/help.html). We give brief descriptions below.

Accession number To search for a range of accession numbers, type X12345 .. X23456. You cal also search on a part of the number: X1234 gives you all accession numbers that start with this string.

Subtype PC users can select multiple subtypes by using 'ctrl-click.' For most other browser/platform combinations, either shift or command will do this. If you are interested in subtypes not included in this list, use the Advanced Search interface, described below.

Sequence Information

Accession number
Sequence name
Sampling country US
Sampling city
Sampling year
Sequence length
Subtype: no subtype, A, A1, A2, B, C
Incl. recombinants
Organism: Any
Incl. problematic seqs: yes no

Patient Information

Patient code
Risk factor: Any
Viral load
CD4 count
Infection country
Infection year
Incl. only sequences from patients with HLA information: yes no
CD8 count

Other Information

Coreceptor: list field in output, only CCR5, all CCR5, only CXCR4, all CXCR4, only RSX4
Author last name
Geographic region: Any
Pubmed/Medline ID
Phenotype: list field in output, NSI, SI
Incl. only drug naive sequences: yes no
Days from seroconversion
Days from infection
# of patient seqs >2

Find all sequences for a specific gene or region

Specific regions of HIV-1 and SIVcpz can be retrieved from the HIV database using the following options:

Include fragments of minimum length 100

Genomic region: 5' LTR U3, 5' LTR U5, TAR, Gag-Pol, Gag, p17 (matrix), p24 (capsid), p7 (nucleocapsid), p6, Pol CDS, p51 (RT), p15 (RNAse H), p31 (integrase), protease

Or define start and end

To retrieve HIV-1 sequences form the database and integrate them into your own sequence alignment, paste your aligned nucleotide sequences into the submission box below.

Or upload your alignment file: Browse...

Output

List 100 records per page Search Reset

Include recombinants By default, recombinants containing fragments of the selected subtype(s) are included in the retrieval; uncheck this box to exclude them.

Authors Searches for author(s) listed on the publication. Do not include initials. You can also search on part of the name, *e.g.*, "James" will find authors with last name James or Jameson.

Pubmed/Medline ID The search returns all sequences associated with a specific PubMed ID. Although Medline IDs are no longer being assigned, they may still be searched and retrieved using this same field.

Patient code The patient code is displayed as a 2-part number, for example "P1(10139520)". The first part is usually the name or number by which the patient is identified in publication(s). The second part is a unique number assigned by our database, the patient ID. A patient code such as "P1" can (and does) refer to more than 1 patient. However, the sequence records associated with "10139520" are

specific to a unique patient.

Risk factor This field describes the risk activity by which the patient most likely was infected.

Infection country We use the official two-letter country code for the infection country. A list of these codes is available on our website.

Infection year The year in which the patient was infected.

Days from infection The number of days from the time the patient was infected until the sample was taken for sequencing.

Days from seroconversion The number of days between the patient's seroconversion and the date the sample was taken for sequencing.

Sampling country The 2-letter code for the country in which the sample was taken.

Sampling year The year in which the sequenced sample was taken.

Geographic region This is a way to retrieve all sequences from (for example) the African continent without having to search for each country separately. Clicking on the field name shows a list of which countries are included in each region.

Genomic region search The user can specify which genomic region to include in the search in three different ways: 1) by predefined region in a table; 2) by HXB2 coordinates; 3) by automatic matching start and stop coordinates to a user provided alignment. Part or all of the sequences are used if they fall within the selected region. A genomic map showing the regions is available on the website. The external sequences are automatically aligned to the search.

Exclude problematic sequences This option excludes certain sequences from results:

- N: high non-ACTG content (N's or IUPAC codes)
- C: potential contamination, as determined by the database staff
- H: hypermutated
- S: synthetic sequence

When searching for sequences by accession number, problematic sequences are included in the results, but their problematic code is indicated; we assume you specifically want these sequences. For other searches, they are excluded by default, but you can include them by unchecking the corresponding boxes.

Other fields This is a pull-down menu to access several other search fields in the database without cluttering the interface. Only one option can be chose per search.

Infection city The city (or region) where the patient was infected.

Title Words from the title of the publication associated with the sequence.

Comment Words in the comments entered by database staff.

Patient sex M or F.

Patient age The patient's age in days at the time of sampling.

Project The name of the project or cohort.

Progression EC, LTNP, SP, RP, or P.

Number of patient sequences Use this field to find patients who have more than # sequences.

Patient health Acute infection, asymptomatic, symptomatic, AIDS, or deceased.

Isolate name Isolate name as given by the authors.

Clone name Clone name as given by the authors.

Sample tissue Material from which the virus was isolated.

Culture method Uncultured, primary [culture], or expanded [culture]

Search results The search results are presented in a table showing some basic information about each sequence. A small graphic for each sequence shows where in the genome it is located. This can be very useful to determine which region is best represented in that set, and therefore most suitable for further analysis.

The search results can be sorted and selected in various ways. Retrieved sequences can be downloaded as an aligned file in FastA or other formats. These alignments need manual inspection and often improvement, but form a very useful starting point. Alternatively, sequences can be downloaded as unaligned nucleotides and/or translated to amino acids in any reading frame.

Make Tree | Download Sequences | Save Background Info | Clear

Displaying 1 - 32 of 32 sequences found

Select all | Unselect all | Invert selection | One sequence/patient | Select record [ ] to [ ] | List 32 records per page

Click on field name to sort in ascending or descending order

#	Select		Patient Code (id)	Accession	Name	Subtype	Country	Sampling Year	# of patient seqs	Genomic Region	Sequence Length	Organism
1	☐	Blast	610185(10140292)	AY140820	610185H	C	US		8		1188	HIV-1
2	☐	Blast	610185(10140292)	AY140821	610185H	C	US		8		1180	HIV-1
3	☐	Blast	610185(10140292)	AY140822	610185H	C	US		8		1180	HIV-1
4	☐	Blast	610185(10140292)	AY140823	610185H	C	US		8		1189	HIV-1
5	☐	Blast	27_5016(10148221)	AY444801	98US_MSC5016	C	US	1998	2		8415	HIV-1
6	☐	Blast	T2(10149045)	AY484347	01US T21tca	C	US	2001	25		559	HIV-1
7	☐	Blast	T2(10149045)	AY484348	01US T21tcb	C	US	2001	25		559	HIV-1
8	☐	Blast	T2(10149045)	AY484349	01US T21tcc	C	US	2001	25		559	HIV-1
9	☐	Blast	T2(10149045)	AY484350	01US T21tcd	C	US	2001	25		559	HIV-1
10	☐	Blast	T2(10149045)	AY484351	01US T21tce	C	US	2001	25		559	HIV-1

The search interface also allows you to download the data in the output table as a tab-delimited file, optionally including the unaligned or aligned sequences. The data can easily be imported into a text editor or a spreadsheet such as Excel.

Sorting the sequences To sort the sequences on the content of one of the columns, click on the title of that column. Clicking again will sort them in the reverse order.

Selecting sequences You can select sequences by checking the boxes at the beginning of the line. To simplify the process, you can also use the blue-on-white buttons at the top of the table. Even if your results are not displayed on a single page, these buttons work across pages. The 'Select all' and 'Unselect all' functions are obvious. Use 'Invert selection' when you want to exclude a few sequences; select those and then invert the selection. That will save a lot of clicking. 'Show all' allows all sequences to be listed on one page. You can use 'Select record __ to __' to select a range of sequences; the numbers refer to the line numbers in the table. Finally, use 'List __ records per page' to change the length of each page.

Limiting the set to 1 sequence per patient This button is only displayed when a genomic region is selected as one of the search criteria. It randomly selects one sequence from all sequences in the search result that share a patient record. In other words, if there are multiple sequences that are known to be from the same patient, all but one are discarded. Note that if multiple sequences per patient are present but no patient record exists, these sequences will be deleted from the set. In other words, this function is dependent on our annotation.

Downloading the sequences aligned vs. unaligned If your set contains only HIV-1 sequences, you can download nucleotide sequences as an alignment, or unaligned. HIV-2 and SIV sequences cannot be pre-aligned because no pre-aligned sequences are stored in the database. Amino acids only come unaligned, in any (or all) of the 3 reading frames.

If you used a genomic region or sequence coordinates to retrieve your alignment and you have checked the 'clip to selected region' box, your sequences will be limited to the selected region. Otherwise, you will end up with an alignment that covers the entire genome including the alignment gaps, i.e. is around 11,000 characters long. This can be convenient if you want to align your sequences to a set of complete genomes, or to other sequences retrieved using the same method (these alignments may differ by a few positions). Note that the alignments are not necessarily optimal and usually require manual adjustment. If you download an alignment, sequences that do not have valid coordinates relative to the reference sequence will not be included in the alignment. Aside from HIV-2 and SIV sequences, this can also happen if the sequences are very short, if they contain non-HIV inserts, or if they are reverse complements. These sequences will be easily noticed in the search interface output because they do not have the icon that shows the location, but say "no location info" instead.

Including a reference sequence or reference alignment You can include the reference sequence HXB2 in your downloaded sequences. This will make it easier to use the SynchAlign tool to align these sequences to other sets.

How the sequences are aligned When the sequences are uploaded into the database, they are internally aligned against a 'model sequence' that represents all sequences that are already present in the database. For this alignment, we use the HMMER program, written by Sean Eddy (http://hmmer.janelia.org/). The start and end coordinates of each sequence relative to the model sequence, as well as the location of all the gaps, are stored in the database. When you request all sequences encompassing the *vif* gene, for example, the coordinates for the *vif* gene in the model sequence are retrieved, and all sequences with a lower (or equal) starting point and a higher (or equal) stopping point are retrieved. When the sequences are downloaded, the gaps relative to the model sequences are inserted. For the little image that shows the location of the sequence relative to the genome, a slightly different set of coordinates is used, relative to the reference sequence (HXB2 or SIVsmm239) instead of the model sequence. These coordinates are produced by an algorithm, and are identical to the coordinates that the Sequence Locator tool produces. The location of some sequences cannot be accurately determined, often because they are too short. In these cases, the sequence will not be included in the aligned download, but if you download the sequences unaligned it will be there.

Creating a phylogenetic tree You can make a neighbor-joining tree from all or a subset of your retrieved sequences, your aligned user sequences, and include subtype reference sequences. The interface allows you to compose labels for your sequences, to choose the evolutionary model for the distance calculation (currently F84, Jukes-Cantor, Tamura/Nei, Kimura 2-parameter, and the General Reversible model), to set gap handling options, to set site rate variation, and to choose the outgroup sequence. The alignment, treefile, and various graphical representations of the tree can be downloaded.

Downloading background information It is possible to download the output shown in the search results table as a tab-delimited file, which allows you to tabulate background data for the retrieved set. Examples of background information: patient information (code, health status, age, gender, risk factor, infection date, infection country, viral load), comments (from the authors or the database staff), and sequence information (sampling city, clone name, etc). These fields can be from any of the fields available from the search interface.

Links within the search results table Several links are located inside the search results table. These links only apply to the sequence on that line.

BLAST does a search of the sequence against the HIV database.

Accession Clicking on this link displays a "GenBank-style" entry that contains all data from GenBank, plus extra features added by our database. You can download the entire sequence or part of it in several formats; there is a link to the original NCBI entry; and there are links to "Show all sequences for reference X". These links use the publication ID to retrieve all sequences that are associated with that publication or sequence deposit. Note: if you wish to display or save the GenBank information for your whole set of selected sequences, go to the "Download sequences" option and choose "GenBank" as the format.

Patient Clicking the patient ID displays all the information available in the databasefor that patient with links to sequences drawn from that patient.

Genomic Region Mousing over the little green-and-yellow icon shows the exact start and stop coordinates of the sequence.

Advanced Search Interface

This interface dynamically reads the schema of the database and generates a graphical overview of the tables and fields. You can use this overview to generate your own custom-made search interface. Just check the boxes next to the fields you want to either search on, or list in the output. However, some of the 'overhead' that the regular interface performs automatically must be done by hand in the advanced interface. For example, when you check fields from multiple tables, you need to make sure that they share a key (shown in red), otherwise the search will fail. You can get information and examples of the content of the tables and fields by mousing over or clicking on the table names.

Make Search Interface Reset

Accession(SA)
- [x] SE id(SA)
- [x] Accession

Sequence sample(SSAM)
- [x] SE id(SSAM)
- [x] PAT id(SSAM)
- [x] Name
- [ ] Locus name
- [ ] Isolate name
- [ ] Clone name
- [x] Country
- [ ] Sampling city
- [x] Sampling year
- [ ] Patient Age
- [ ] Patient health
- [ ] Organism
- [x] Subtype
- [ ] Phenotype
- [ ] Coreceptor
- [ ] Sample tissue
- [ ] Culture method
- [ ] Sequencing method
- [ ] Molecule type
- [ ] Georegion
- [x] Drug naive
- [x] Problematic
- [ ] Viral load
- [ ] CD4 count
- [ ] CD8 count
- [ ] Sampling year delta
- [ ] Days post infection
- [ ] Days from seroconversion

Patient(PAT)
- [ ] PAT id
- [ ] Patient code
- [ ] Patient sex
- [ ] Risk factor
- [ ] Infection country
- [ ] Infection city
- [ ] Infection year
- [ ] Patient comment
- [ ] HLA type
- [ ] Project
- [ ] Patient ethnicity
- [ ] Infection year delta
- [ ] Progression
- [ ] Patient cohort
- [ ] # of patient seqs

In the example shown here, we are going to make a search interface where we can retrieve all sequences covering Pol protease and RT (coordinates 2253–3870) from patients that are known to be non-drug-naïve. We have checked several additional fields so that we can view these fields in the output.

When you have made your selection of fields, click the "Search interface" button, and a search interface will be generated, shown on the following page. This interface looks much like the standard search interface, but it will contain exactly the fields you selected. You can search on any of the fields, and all fields included in the search interface will be listed in the output. You can also set the number of search results you want to list per page.

The results page from the Advance Search looks similar to the results page from the Regular Search, but with fewer options. You can sort on any of the fields, and download the sequences and/or the background information. Note in the example shown, that including the "Problematic" field in the search allows us to see that one of the sequences is a hypermutant.

Accession(SA)

SE id(SA) Any | Accession Any

Sequence map(SM)

SE id(SM) Any | HXB2 start Any

HXB2 stop Any

Sequence sample(SSAM)

SE id(SSAM) Any | PAT id(SSAM) Any

Name Any | Country [UNITED STATES] [URUGUAY] [UZBEKISTAN]

Sampling year Any [1959] [1975] | Subtype [BLU] [BU] [C]

Drug naive Any [NULL] [no] | Problematic Any [0] [C]

List 100 records per page, order by SE id(SA) ascending | Search | Reset

Show results selected

Custom search interface (above) based on the selections specified on the previous page. The results page (below) is similar to the standard results.

Displaying 1 - 10 of 72 sequences found:

Select all | Unselect all | Invert selection | Show all | List 10 records per page

Retrieve All sequences in Fasta format: | Show names as Subtype Country Year Name

only for HIV-1: (Align sequences) Include HXB2 Reference Sequence (K03455) | Download Nucleotides

#Select	PAT id	# of patient seqs	SE id(SA)	Accession	SE id(SSAM)	PAT id(SSAM)	Name	Country	Sampling year	Subtype	Drug naive	Problematic
1	10140292	8	151026(BLAST)	AY140820	151026	10140292	610185H	UNITED STATES		C		0
2	10140292	8	151025(BLAST)	AY140821	151025	10140292	610185H	UNITED STATES		C		0
3	10140292	8	151024(BLAST)	AY140822	151024	10140292	610185H	UNITED STATES		C		0
4	10140292	8	151023(BLAST)	AY140823	151023	10140292	610185H	UNITED STATES		C		0
5	10140292	8	151010(BLAST)	AY140836	151010	10140292	610185H	UNITED STATES		C		0
6	10140292	8	151009(BLAST)	AY140837	151009	10140292	610185H	UNITED STATES		C		0
7	10140292	8	151008(BLAST)	AY140838	151008	10140292	610185H	UNITED STATES		C		0
8	10140292	8	151007(BLAST)	AY140839	151007	10140292	610185H	UNITED STATES		C		0
9	10149043	39	165781(BLAST)	AY483953	165781	10149043	01UST11sc1	UNITED STATES	2001	C	no	0
10	10149043	39	165780(BLAST)	AY483954	165780	10149043	01UST11sc3	UNITED STATES	2001	C	no	0

Next | Last

Download tab-delimited results, include sequence

Advantages of advanced search interface:

• Advanced search allows additional types of searches not possible on the regular interface. As one example, you could restrict your search to include only samples from non-drug-naive patients.

• You can search and view data from all available fields, including multiple fields that appear under "Other Fields" in the regular interface.

• You can specifically select sequences that have a "null" value (no data) in specific fields.

Limitations of advanced search interface:

• The search output does not directly interface with TreeBuilder. To make a phylogenetic tree, export your aligned sequences in FastA format, then use them as input in the TreeMaker tool.

• Options for searching for a specific genomic region are limited.

• Problematic sequences are not removed by default. You will not see any indication of which sequences are problematic unless you include this field in your search.

Other differences from the standard search interface:

• Searches are limited to 10,000 results. If your search produces more than this, it will fail. Restrict your search to produce fewer results.

• To retrieve sequences from part of the genome, *e.g*., all *vpu* sequences, you need to find the HXB2 coordinates for *vpu* (6062–6310), and then search for HXB2 start < 6062 and HXB2 end> 6310. It is not possible to include sequence fragments smaller than that range.

• The advanced search interface is case-sensitive; it does distinguish between lower- and upper-case letters. When searching on text fields, if you unexpectedly get no hits, try UPPERCASing and/or adding an * to the search. Adding an * will turn the search into a case-insensitive wildcard search. Note that the * will only expand in its own location, so if you want to search for a string in the middle of two unknown other stings, use *string*.

• When you generate your customized search interface, all fields are pre-filled with "ANY". This will display what is entered in that field (even if blank), but will not restrict the search. If you remove the word "ANY", you will restrict the search to entries that have no data in the field (see next point).

Geography Search Interface

The Geography tool is another way to select sequences from the database. It can be used to find the number of sequences of each genotype within any selected geographical region. The information can be extracted as a graphic map, as a table of data, or as a list of specific sequences. The list of sequences connects with the search interface to allow rapid retrieval and analysis of the sequences that are displayed. This tool can be very useful to get a general idea of what genotypes have been found in what countries, as well as the density of sampling in different regions of the world.

Data can be extracted for the whole world, for a region, or for any specific country. The regions available to search are: Africa, Asia, Caribbean, Central America, Europe, Former USSR, Middle East, North America, Oceania, South America, and Sub-Saharan Africa. Note that some of these regions are overlapping, such as Africa and sub-Saharan Africa. A complete list of what countries are included within each region is available (hiv.lanl.gov/content/hiv-db/HelpDocs/geo_regions.html).

Searches can be limited to either HIV-1 or HIV-2. Data can be extracted for the whole world, for a region, or for any specific country. Search results include all sequences, regardless of their length or location within the HIV genome. Search results exclude sequences for which the database lacks an annotation of subtype or country, and sequences annotated as "problematic".

Performing a search To run the search, select HIV-1 or HIV-2 and the desired geographic region. Only 1 region or country may be selected for each search. Click "Show all", "show non-recombinant" or "show recombinant". The resulting page displays a pie chart of the sequence subtypes in the region or country of interest. From here you have the following options:

• View the pie chart. You can use the "save image" function of your browser to save this image as a PNG file, if desired.

• Click on an individual country within a region to obtain the data from that country (this applies only to searches of regions).

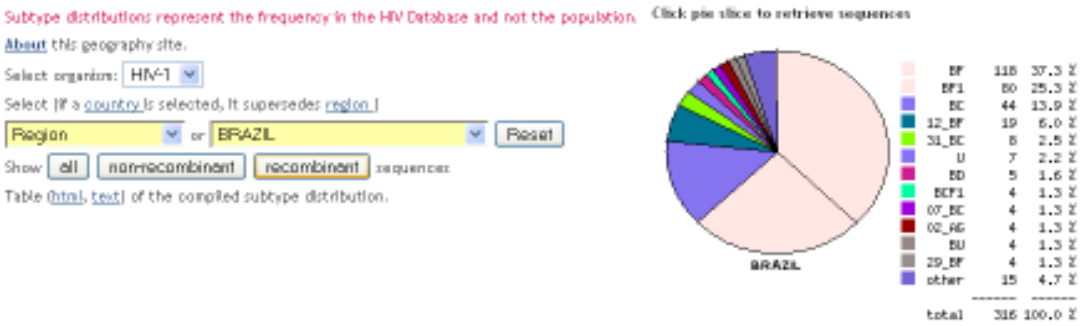
• Click on "Table (html)" to go to a page with a table showing the number of sequences with each subtype.

• Click on "Table (text)" to download a space-delimited text file of the subtype distribution data. This text file can be opened in a spreadsheet program.

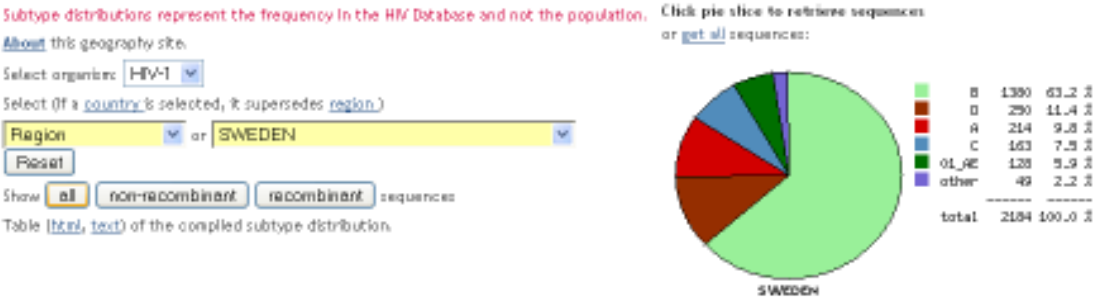
• Click on "get all" or click on any specific slice of the pie chart. These options take you to a list of the sequence accession numbers. This list is in exactly the same as the list of sequences you would get from the regular sequence Search Interface. From this list, you have many options: Make Tree, Download Sequences, or Save Background Information. The options from this page are explained above in detail in the explanation for the Regular Search Interface.

Examples of geography searches Perhaps the best way to understand the possibilities offered by this interface is to look at some specific examples of hypothetical questions you could answer with this tool.

1. *What are some CRFs that commonly occur in sequences from Brazil?* Select HIV-1/Brazil and click the "Show recombinant sequences" button. The resulting pie chart shows just the CRF and other recombinant sequences sampled in Brazil. To see what subtypes are represented in the "Other" category, click the corresponding pie slice, and you will see them listed.



2. *What are the rarest HIV-1 sequence subtypes ever sampled in Sweden?* This is a search that would be difficult using the regular Search Interface, but easy here. Select HIV-1/Sweden and "Show all". In the resulting pie chart, click on the "Other" slice. The resulting list (see below) shows the subtypes of the sequences that were too rare to display as separate pie slices.



Limitations and additional details There is some redundancy in the information that can be extracted by the Geography Search and the regular Search Interface. For example, if you want to extract all subtype B HIV-1 sequences from Africa, you could use either interface. The main reason that you may prefer to do the search using the Geography Search is to see a graphic presentation of all the genotypes. The graphic output may provide some interesting insights that you would not notice in the lists obtained from the sequence Search Interface. However, if the objective is only to extract sequences of a single subtype, regardless of the geographic distribution of that subtype or the representation of that subtype relative to others, then the regular Search Interface may be the better option.

The results from this tool need to be interpreted with care: it is easy to overlook the sampling biases that can distort the frequencies of sequences in the database relative to those in the population. Do not draw conclusions about the epidemiology of HIV-1 from the subtype distribution presented here. The data stored in the database are taken from publications in the literature, and in general, there is no epidemiological framework - the database is just a listing of available sequences. Many studies focus on rarer subtypes and recombinants, and this tends to cause overrepresentation of such sequences. Furthermore, the distribution shown on the maps is based only on the country of sequence isolation, which is not always the country of infection. While the results of this tool are not particularly helpful for epidemiological purposes, one can still use the tool to get a sense of how intensively a region has been studied and a rough indication of the subtype distributions.

The data generated by this search are only as good as the annotation of the sequences in the database. There can be errors in the subtyping of sequences, so all results should be interpreted carefully. When examining rare subtypes, it may be worthwhile to verify the correct subtyping of specific sequences. Furthermore, not all the sequences in the HIV sequence database have an assigned subtype. At the time of this writing, approximately 15% of all sequences in the database have no annotation of subtype. Sequences where the subtype field is blank are not reported in the output from this tool.

Small sample sizes can also be problem with this tool. In countries where there are few subtyped sequences, one or a few studies (with whatever their objectives may have been) will determine the output. This is particularly true for HIV-2, for which far fewer sequences are available than for HIV-1.

This tool lumps together sequences that are annotated with certain sub-subtypes. For example, the sequences listed as subtype “A” from this tool include all sequences annotated as “A”, “A1”, or “A2”. Sequences listed as subtype “F” from this tool include all sequences annotated as “F”, “F1”, or “F2”. However, sub-subtypes that are part of recombinants are not lumped together. For example, “BF”, “BF1”, and “BF2” are graphed separately.

III. IMMUNOLOGY DATABASE

The HIV immunology database provides resources for scientists working with immunological responses to HIV. The database contains a wealth of curated information about HIV T-cell epitopes and antibody binding sites. Currently the HIV immunology database contains 3818 cytotoxic T-cell (CTL) epitope entries, 829 T-helper epitope entries, 1366 antibody entries, and a total of 1895 publications. New entries are added and proofread continually, and existing ones are updated as needed.

The data included in HIV immunology database are extracted from published HIV immunology literature. HIV-specific B-cell and T-cell responses are summarized and annotated. Immunological responses are divided into 3 sections of the database: CTL (CD8+), T helper (CD4+), and antibody (Ab). Within these sections, defined epitopes are organized by protein and binding sites within each protein, moving from left to right through the coding regions of the HIV genome. We include human responses to natural HIV infections, as well as vaccine studies in humans and a range of animal models. Responses that are not specifically defined, such as responses to whole proteins or monoclonal antibody responses to discontinuous epitopes, are summarized at the end of each protein sub-section. Studies describing general human responses to HIV, but not to any specific protein, are included at the end of each section.

The annotation of database entries includes information such as cross-reactivity, escape mutations, antibody sequence, TCR usage, functional domains that overlap with an epitope, immune response associations with rates of progression and therapy, and how specific epitopes were experimentally defined. Basic information such as HLA specificities for T-cell epitopes, isotypes of monoclonal antibodies, and epitope sequences are included whenever possible. In addition, the HIV immunology database includes tables, maps, alignments of HIV-specific CTL, helper and antibody epitopes, antibody indices, and simple web-based tools with the goal of assisting immunologists in experimental design and interpretation of their results.

An important distinction between the T-cell and antibody entries is that a single T-cell epitope can have multiple entries; generally each entry represents a single publication. In contrast, each monoclonal

antibody (MAb) has a single entry that includes all publications we could find that refer to the use of this specific monoclonal antibody.

CTL (CD8+) and T-helper (CD4+) Searches

CTL (CD8+) and T-helper (CD4+) epitope database sections are organized identically and so are described together here. It is important to note that although these are separate sections, the simple distinctions between CTL and helper T cells have become blurred as more is learned about the range of responses triggered in CD4 and CD8 positive T-cells. When adding the most recent studies, we have tried to place T-cell responses in a reasonable manner into our traditional T-helper and CTL sections, and to specify the assay used to measure the response in each study.

The following is a list of fields and links in T-cell epitope entries:

Record number A unique number assigned by the database, in approximate order of entry. This number should be cited if you send us comments or questions about an entry.

HXB2 Location The position of the defined epitope location is given relative to the protein sequence of HXB2. Because of HIV-1 variation, the epitope may not actually be present in HXB2, rather the position in HXB2 indicates the position aligned to the epitope. The viral strain HXB2 (GenBank Accession Number K03455) is used as a reference strain throughout the database. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2 proteins are available. The precise positions of any epitope relative to the HXB2 reference strain can be readily obtained using the interactive position locator at our web site: http://hiv-web.lanl.gov/content/hiv-db/LOCATE/locate.html

Author Location The amino acid positions of the epitope boundaries relative to the reference sequence are listed, as given in the primary publication. Frequently, these positions are imprecise or are based on a non-HXB2 strain. Thus, these locations do not always match the HXB2 numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein.

Subtype The subtype under study; generally not specified for B subtype.

Epitope Sequence The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On occasions when only the position numbers and not the actual peptide sequence was specified in the original publication, we try to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may misrepresent the epitope sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication are followed by a question mark in the table.

Epitope Name The epitope's name if attributed by the publication, *e.g.*, "SL9".

Species (MHC/HLA) The species responding (*e.g.*, chimpanzee, mouse), and MHC or HLA specificity of the epitope, as described in the primary publication (*e.g.*, A*0201).

Immunogen The antigenic stimulus that generated the initial immune response, *e.g.*, HIV infection or vaccine. If a vaccine stimulated the response, additional fields are available that describe the vaccine.

Vaccine type The vaccine construct and boost.

Vaccine strain The strain of HIV or SHIV used for the antigen.

Vaccine component The HIV protein (complete or partial) included in the vaccine.

Adjuvant Stimulatory agent sometimes included in a vaccine formulation to enhance or modify the immune-stimulating properties of a vaccine.

Country The country from which the samples were obtained; generally not specified if the study was conducted in the United States.

Experimental methods The methods used by the authors to test the immune response (for example T-cell Elispot, intracellular cytokine staining, etc.).

Keywords A searchable field for the web interface to help identify entries of particular interest.

Notes Brief descriptions of what was learned about the T-cell response from the study. Examples of the kinds of things included: correlation with survival in longitudinal studies, immune escape, quantitative features of the response, subtype cross-reactivity, etc.

Reference The primary reference linked to PubMed.

The CTL and T-helper search interfaces, shown below, allow you to search using the following fields: HIV protein (separately for defined and undefined epitopes), epitope sequence, subtype, immunogen, vaccine details, species, MHC/HLA, author (any one author from primary publication), country, and keywords.

HIV Immunology CTL, CD8+ T-Cell, Search

HIV Protein	Proteins with defined epitopes: - ALL -, p17, p17-p24, p24, p24-p2p7p1p6 Proteins with undefined epitopes: - ALL -, Gag, Gag/Pol, Protease-RT, Pol
Epitope	
Subtype	- ALL -
Immunogen	- ALL -, computer prediction, HIV-1 and HCV co-infection, HIV-1 exposed seronegative, HIV-1 infected monocyte-derived, HIV-1 infection, HIV-1 or HIV-2 infection
Vaccine details	If Immunogen is Vaccine, additional search details Vaccine type: - ALL - Vaccine strain: - ALL - Vaccine component: - ALL - Adjuvant: - ALL -
Species	- ALL -
MHC/HLA	- ALL -, - NULL -, A*0101, A*02, A*0201, A*0201, A*0205, A*0201, B*3501
Author	First Last
Country	- ALL -
Keywords	- ALL -, acute/early infection, adjuvant comparison, antibody generation, assay standardization/improvement, binding affinity, characterizing CD8+ T cells

Antibody Search

The antibody database summarizes HIV-specific antibodies (Abs) arranged sequentially according to the location of their binding domain. Monoclonal antibodies (Mabs) that do not bind to defined linear peptides are grouped by category at the end of each protein. Antibody categories (e.g., CD4 binding site (CD4BS) antibodies) are also noted in an index in the compendium. Studies of polyclonal Ab responses are also included. Responses that are just characterized by binding to a protein, with no known specific binding site, are listed at the end of each protein section in the compendium.

Each MAb or polyclonal response has a multipart basic entry that includes all publications that refer to the use of that specific Ab. Most of the fields are similar to the corresponding fields for T-cell epitopes, such as record number, HXB2 location of the binding site, author location, epitope sequence, and immunogen (the antigenic stimulus of the original B-cell response). The fields that differ or are

specific to antibody entries include the following.

MAb ID The name of the monoclonal antibody with synonyms in parentheses. MAbs often have several names. For example, punctuation can be lost and names are often shortened (M-70 in one paper can be M70 in another). Polyclonal responses are listed as "polyclonal" in this field.

Neutralizing L: neutralizes lab strains. P: neutralizes at least some primary isolates. no: does not neutralize. No information in this field means that neutralization was either not discussed or unresolved in the primary publications referring to the MAb.

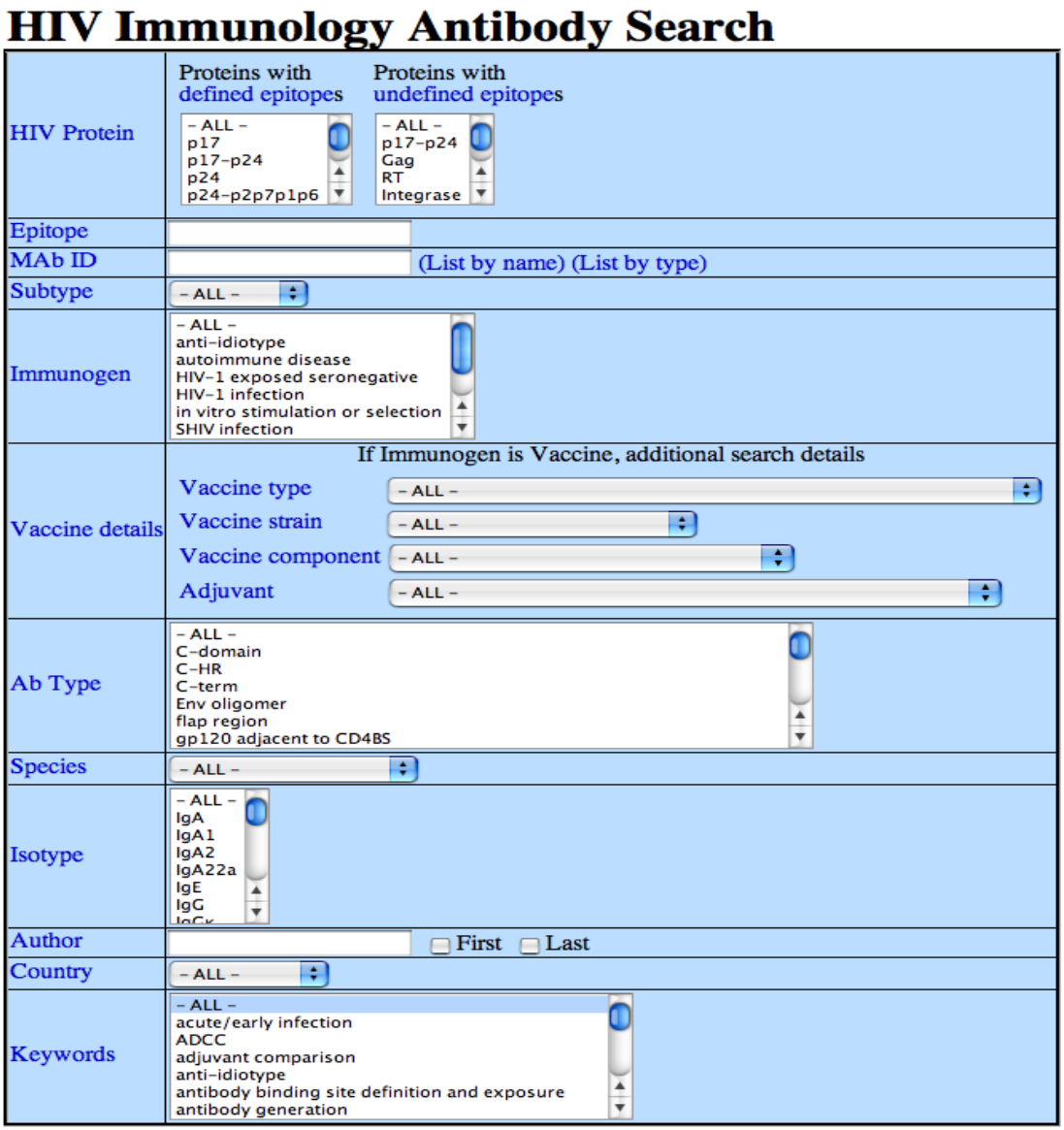
Species(Isotype) The host that the antibody was generated in, and the isotype of the antibody.

Donor Information about who produced the Ab, where to obtain it, and to whom to provide credit.

References All publications that we could find that refer to the use of a specific Ab.

Notes Describe the context of each study and what was learned about the antibody.

The antibody search interface, shown below, allows you to search using the following fields: HIV protein (separately for defined and undefined epitopes), epitope sequence, subtype, immunogen, vaccine details, species, MAb ID, author (any one author from primary publication), Ab type, country, and keywords.



IV. VACCINE TRIALS DATABASE

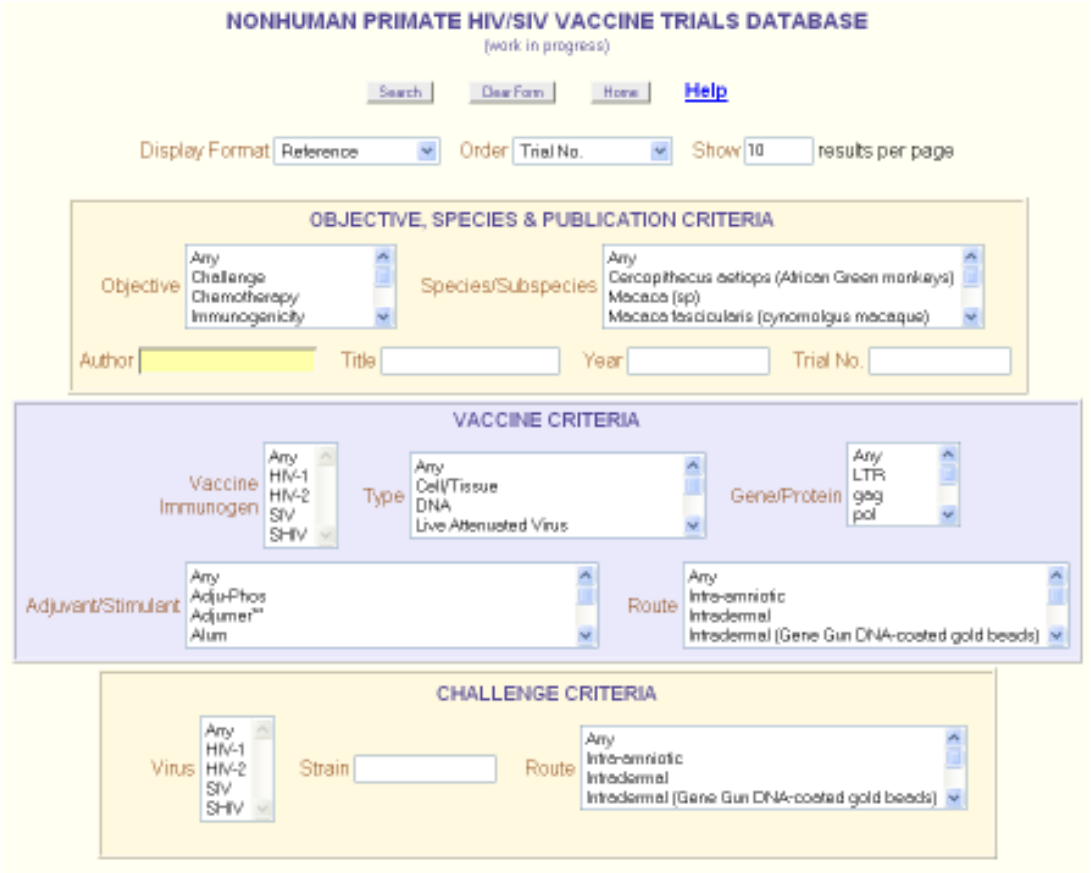
The HIV/SIV Vaccine Trials Database (www.hiv.lanl.gov/content/vaccine/home.html) contains data on studies of HIV/SIV vaccine trials in nonhuman primates. This database is a tool for compilation, search, and comparison of published studies. We use a set of criteria to scan PubMed for relevant studies to enter into the database. In selecting studies for entry, priority is given to recently published studies in journals generally regarded as the primary source of information pertaining to HIV and SIV vaccine research in nonhuman primates. In most cases, we give priority to challenge studies, where the animals received a live virus to measure the 'efficacy' of the immunogen(s) inoculated during the course of the investigation.

Prior to the development of this database, Dr. Jon Warren at the EMMES Corporation had maintained a similar database, though organized differently, and with different data fields and somewhat different nomenclature. The studies in that database include many published through 1999 and can be accessed in the current Los Alamos Vaccine Trials Database. All of the search criteria on the search form apply to the studies entered at Los Alamos (referred to as the "Current Database"), and *most* criteria apply to the data collected by Jon Warren (referred to as the "Previous Database").

The vaccine trials database can be searched in 2 ways, via a conventional search form, and via a cross-table form. In addition, there is a separate search tool to access a database of vaccine adjuvants.

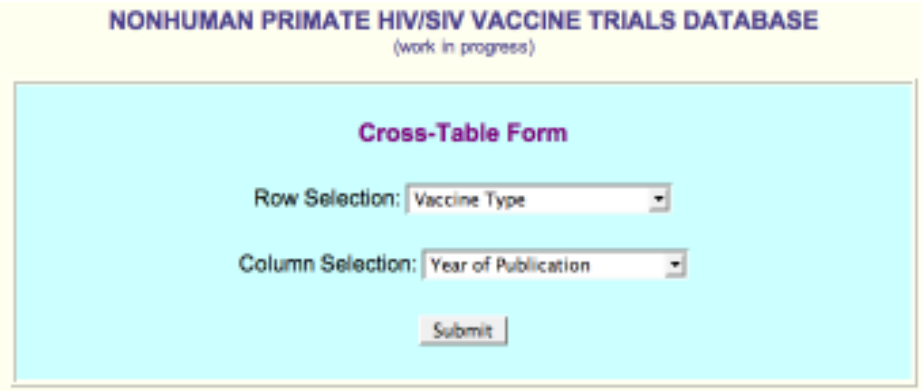
Search Form

The conventional search form allows you to select trials according to the combined values of 14 separate criteria such as vaccine type, vaccine route, challenge strain, etc. The matching trials can then be displayed in various formats, and detailed information about the trial, such as details on the substances and groups used, are also available. To display all available results, be sure to click "View Trials in Previous Database".



Cross-Table Form

The cross-table form provides a unique way to explore trial data by presenting counts and results (number of case animals protected from infection and total number of case animals) by the relationship of two selected values displayed in a matrix, for example vaccine type by year.



The results will show how many trials were done for each vaccine type in each year. Clicking on the number in the matrix takes you to a list of those trials that compose a result cell.

Vaccine Type x Year of Publication

5/25/07 9:37

Vaccine Type	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Cell/Tissue	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 [4/21]
DNA	0	0	1	0	2 [5/6]	0	0	0	0	0	2 [3/3]	0	4	12 [8/57]	13 [15/39]	13 [4/65]	12 [6/38]
Live Attenuated Virus	0	0	0	1 [0/3]	0	1 [4/8]	0	0	0	2 [8/12]	2 [1/4]	1	7 [23/60]	11 [1/36]	3 [3/6]	2 [7/12]	5 [4/27]
Live Virus	0	0	0	0	0	0	0	0	0	2 [7/8]	1	0	1	2 [4/8]	3 [7/18]	1 [3/8]	2 [0/28]
Other	0	0	0	0	1 [2/2]	0	0	0	0	0	0	0	0	1	0	2 [3/16]	0
Passive Antibody	1	1 [0/4]	0	0	2 [6/11]	2 [2/2]	0	0	0	0	1 [3/4]	0	6	3 [8/14]	2 [6/18]	2 [10/15]	3 [5/27]
Purified Viral Products	0	0	1	0	0	2	0	0	0	0	2	0	4	3 [3/27]	3 [5/21]	4 [1/26]	3 [3/16]
Recombinant Live Attenuated Virus	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Recombinant Subunit Protein	0	1	0	1	2 [1/3]	1	1	0	1 [1/3]	4 [8/17]	0	4 [5/11]	2 [13/24]	4	5 [6/28]	2	5 [0/33]
Recombinant Vector (virus/bacteria)	0	0	0	0	1	2	0	0	0	1	2	2 [1/3]	6 [15/29]	9 [5/60]	10 [2/34]	14 [2/59]	17 [0/83]
Synthetic Protein/Peptide	0	0	0	0	0	0	0	0	0	0	1	1 [4/8]	0	2 [0/2]	4 [2/28]	1 [0/8]	1
Virus-like Particle	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1 [3/10]	1
Whole (killed) Inactivated Virus	0	0	4 [13/22]	4 [4/16]	0	3 [8/19]	3 [3/11]	0	0	0	0	2	2	0	0	0	1

Like the search form, this search directly retrieves only sequences in the “Current” database; the number presented in each cell of the table represents only the studies in the current database. In order to view entries from both the current and previous databases, click the number in the cell. Even if the number in the cell is 0, you may still find some relevant studies by clicking the cell and going to the “View Trials in Previous Database” link.

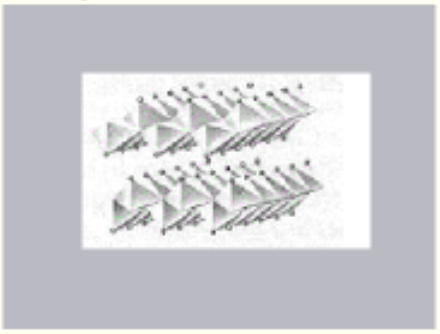
Adjuvant/Stimulant Search

The vaccine database also contains a database of adjuvants used in vaccine trials. To access this information, select the "Adjuvants/Stimulants" link from the main menu. Links from the resulting table take you to details about the structure, properties, uses, and references for each substance. The example below shows some of the information given for the adjuvant alum.

Adjuvant / Stimulant: Alum

Other Names: Alhydrogel; Aluminum hydroxide gel;

Structure: Crystalline aluminum oxyhydroxide AlOOH, known mineralogically as boehmite. The structure consists of corrugated sheets of aluminum octahedra.



Adjuvant Properties: Alhydrogel is the standard preparations for immunological research on aluminum hydroxide gels. The use of aluminum adjuvants is accompanied by stimulation of IL-4 and stimulation of the T-helper-2 subsets in mice, with enhanced IgG1 and IgE production. Further immunomodu) ation is accomplished by the aluminum content. Properties are described in:

- Shirodkar. S., et al., 1990, Aluminum compounds used as adjuvant in vaccines, Phar7n. Res. 7: 1282 1288.
- Stewart-Tull, D. E. S., 1989, Recommendations for the assessment of adjuvants (immunomodulators), in: Immunological Adjuvants and Vaccines (Gregoriadis, G., Allison, A. C., and Poste. G., eds.), PlenumPress, New York, pp. 213-226.
- Gupta, R., et al.. Chapter 8, this volume. 9
- Seeber, S., et al., 199 1, Predicting the adsorption of proteins by aluminum-containing adjuvants, Vaccine 9: 201-203.
- Seeber, S. J., et al., 199 1, Solubilization of aluminum-containing adjuvants by constituents of interstitial fluid. J. Parenteral Sri, Tech. 45: 156-159.
- Hem, S., and White, J. L., Chapter 9, this volume.
- Lindblad, E. B. Aluminum adjuvants, in: The Theory and Practical Application of Adjuvants, chapter 2, (Stewart-Tull, ed.), Wiley & Sons, New York, NY (1995).

Source: Obtained by precipitation of aluminum hydroxide under alkaline conditions.

Uses: Human applications: diphtheria, tetanus, and pertussis vaccines. Veterinary vaccine applications.

Appearance: White gelatinous precipitate in aqueous suspension.

Molecular Weight: Not applicable.

Recommended Storage: 4-25°C. Never expose to freezing. Recommended 2 year shelf life.

Chemical/Physical Properties: Primary particles have a rodlike or fibril morphology and a high surface area. The isoelectric point is 11. Its high surface area gives it a high adsorptive capacity for antigen. Poorly soluble in solutions containing citrate ions. Normal particle size range 0.5-1 Opm.

Incompatibility: Dissolves in strong bases and acids.

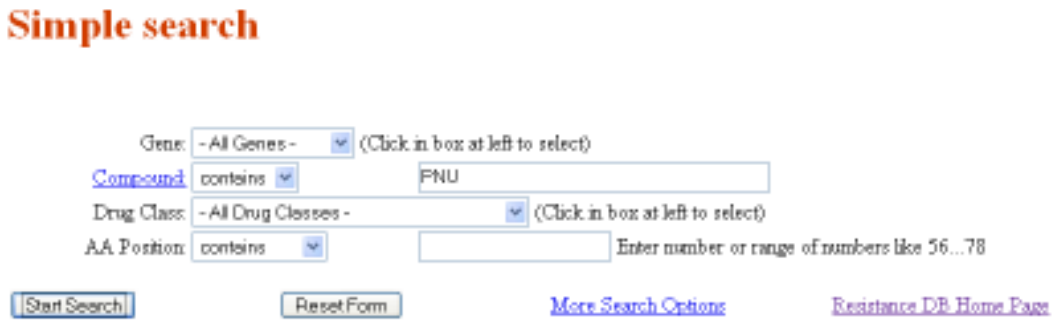
Safety/Toxicity: May cause mild local reactions at the site of injection (erythemas and/ or mild transient swellings).

V. HIV DRUG RESISTANCE DATABASE

The Los Alamos HIV Drug Resistance Database (http://resdb.lanl.gov) contains two pages from which searches can be made for mutations known from the literature to confer resistance to a variety of antiretroviral drugs. This database is updated annually with input provided by Dr. John Mellors and his staff at the University of Pittsburgh.

Simple search

On the simple search page, the searchable fields include gene, compound, drug class, and amino acid position. In the example shown here, the user is searching for mutations in all genes and at any positions associated with compounds that contain the "word" PNU.



This search produces the results page illustrated below.

Records: 1 through 10 of 17 records in database.

Gene (Click for details)	Drug Class	Compound	AA Mutation	Codon Mutation	Cite
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	L 10 F	CTC -> TTC	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	I 13 V	ATA -> GTA	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	V 32 I	GTA -> ATA	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	L 33 F	TTA -> TTT	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	M 36 I	ATG -> ATA	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	K 45 I	AAA -> ATA	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	I 54 V	ATC -> GTC	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	A 71 V	GCT -> GTT	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	V 82 L	GTC -> CTC	Doyon05
HIV-1 Protease	Protease inhibitor	PNU-140690 (tipranavir)	I 84 V	ATA -> GTA	Doyon05

Forward Go Last Find Home

A tabular output shows several basic fields for 10 of the 16 mutations for the compound PNU-140690 (tipranavir). To see the next 6 records, press the Forward button. To see more detailed information about any particular mutation, click on the blue link in the first column "HIV-1 Protease", which takes you to the "record detail" layout shown on the next page.

All information in the database about this mutation is displayed in this view. There is a link to the PubMed entry for the citation associated with this mutation.

Gene: **HIV-1 Protease** DrugClass: Protease inhibitor

Compound: **PNU-140690 (tipranavir)** Synonyms: PNU-140690, tipranavir, U-140690

AAMutation: **L 10 F** Codon mutation: CTC -> TTC

In Vitro: Y In Vivo:? Selected or CrossResist: Selected

Comment: After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir

---

L. Doyon, S. Tremblay, L. Bourgon, E. Wardrop, M.G. Cordingley
Selection and characterization of HIV-1 showing reduced susceptibility to the non-peptidic protease inhibitor tipranavir
Antiviral Res **68(1)**: 27-35 (2005) Medline link: 16122817

Press the **Back** button in your browser to return to table view, or Find

Advanced search

The advanced search page gives you a much wider range of fields on which to search. The illustration below shows a search for protease mutations whose author list contains the name "Condra". (Fourteen records are found.) The layout and information presented on the results pages for the advanced search are identical to those in the simple search.

Advanced search

Gene: HIV-1 Protease In Vitro:
DrugClass: - All Drug Classes - In Vivo:
Compound: contains Cite:
AA Position: Enter number, or range, e.g. 56...78 MedlineID:
Wild Type AA: - No Selection - authors: Condra
Mutant AA: - No Selection - title:
Wild Type Codon: equals journal:
Mutant Codon: equals pub year:

Connect search items with: AND OR Sort by: AAPosition ascending

Start Search | Show All Records | Reset this form

Return to Home Page

ADRA

ADRA, the Antiretroviral Drug Resistance Analysis site (http://www.hiv.lanl.gov/content/hiv-db/ADRA/adra2.html), can be considered both a method of sequence analysis and a search tool. Given a query sequence as input, ADRA scans the sequence to identify the presence of mutations known to confer resistance to antiretroviral drugs. ADRA includes both drugs of clinical significance and compounds that are not clinically validated.

Input ADRA requires a query sequence, either pasted in, or uploaded from a file. The user should specify whether this query is nucleotide or protein, and should select a reference sequence against which to compare the query.

Output

Mutation table ADRA produces a table, reproduced in part below, of mutations found in the query sequence ordered by amino acid position.

Download text file

Sequence Name	vwxyz_frame1
identified gene region(s)	Protease, RT
HXB2r positions*	56 - 479

* indicates amino acid position

- **Table of mutations potentially conferring resistance** (relative to HXB2r)

Protein	aa change	codon change	fold resist	cross resist	compound	record
Protease	L10I	CTC / ATC	ND	ND	MK-639 (L-735,524, indinavir)	view
Protease	L10I	CTC / ATC	ND	ND	Ro 31-8959 (saquinavir)	view
Protease	K20R	AAG / AAA	ND	ND	ABT-538 (ritonavir)	view
Protease	K20R	AAG / AAA	ND	Ro-31-8959 (8);	MK-639 (L-735,524, indinavir)	view
Protease	M36I	ATG / ATA	ND	ND	ABT-538 (ritonavir)	view
Protease	M36I	ATG / ATA	ND	ND	AG1343 (nelfinavir)	view
Protease	I54V	ATA / GTA	ND	ND	Ro 31-8959 (saquinavir)	view
Protease	I54V	ATC / GTC	ND	ND	ABT-538 (ritonavir)	view
Protease	I54V	ATC / GTC	ND	ND	MK-639 (L-735,524, indinavir)	view

The columns are self-explanatory. The last column labeled "record" provides a hyperlink to each mutation's detailed record in the resistance database. Clicking on the view link for the first mutation (L 10 I) brings up a view of this record.

Gene: HIV-1 Protease
Compound: MK-639 (indinavir)
AAMutation: L 10 I
In Vitro: N In Vivo:Y
Comment:

DrugClass: Protease Inhibitor
Synonyms: MK-639, indinavir, crixivan, L735,524
Codon mutation: CTC -> ATC
Selected or CrossResist: Selected

Condra JH, Holder DJ, Schleif WA, Blahy OM, Danovich RM, Gabryelski LJ, Graham DJ, Laird D, Quintero JC, Rhodes A, Robbins HL, Roth E, Shivaprakash M, Yang T, Chodakewitz JA, Deutsch PJ, Leavitt RY, Massari FE, Mellors JW, Squires KE, Steigbigel RT, Teppler H, Emini EA
Genetic correlates of in vivo viral resistance to indinavir, a human immunodeficiency virus type 1 protease inhibitor
J Virol 70(12): 8270-6 (1996) Medline link: 8970946

Summary statement Following the table of mutations is a compilation of drugs or drug combinations to which the query sequence may possess a degree of resistance (shown at the top of the figure below).

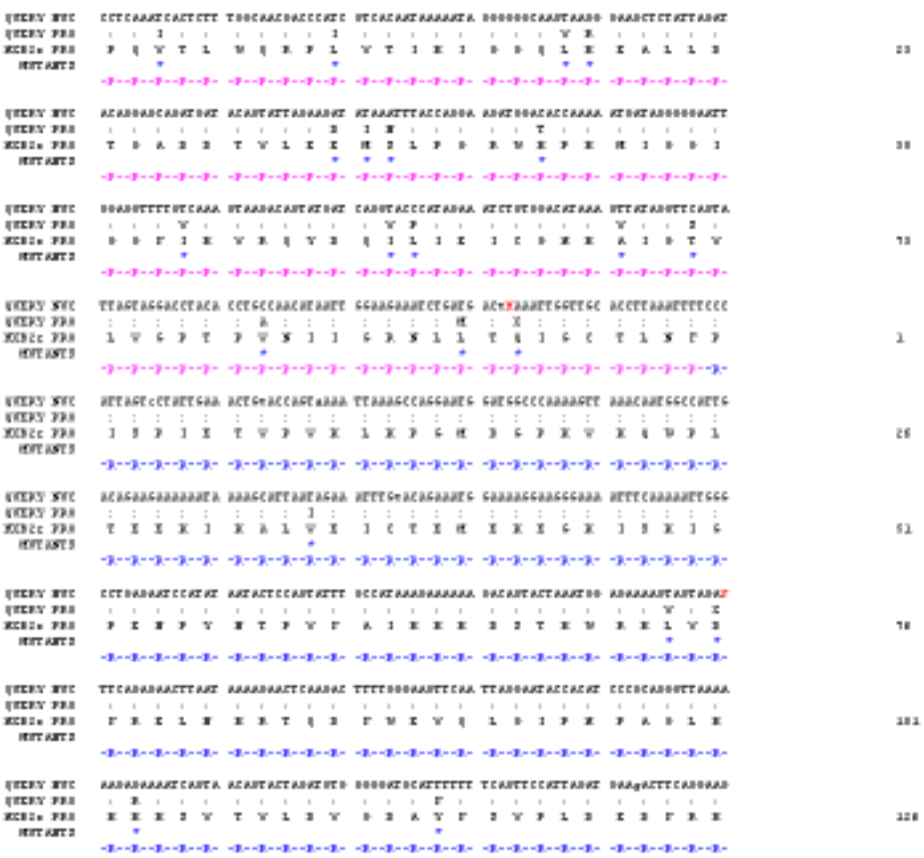
Bear in mind it is inappropriate to use these results in clinical decisions about antiretroviral therapy. Only a minority of entries in the table have been clinically validated. This tool merely provides a summary of links between mutations and drugs defined in the literature.

Alignment Finally, an alignment of the user's query to the reference protein is presented. Mutations are indicated by asterisks (*).

This sequence may be associated with a degree of resistance to these drugs or drug combinations: Nelfinavir; 3TC (lamivudine); SC-52151; (+)dOTC; L-FddC; DXG; BMS 186,318; HBY 097; SKF108922; A-77003; Trovirdine; ddC; ADAMIII; TIBO R82913; AZT + 3TC; (-)dOTC; QM96521; UC-10 (645129); MKC442 (1-EBU); ddI; dOTC (BCH-10652); BILA 1906 BS; BILA 2185 BS; MK-639 (L-735,524, indinavir); Ro 31-8959 (saquinavir); 1592U89; XM323; ABT-538 (ritonavir); P9941; DMP 266 (L-743,726); L-697,661; AG1343 (nelfinavir); BILA 2011 (palinavir); (-)-FTC;

*ALIGNMENT

P delineates the Protease gene region
R delineates the RT gene region
I delineates the Integrase gene region



Mutations in Retroviral Genes Associated with Drug Resistance

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Introduction

Drug resistance is the inevitable consequence of incomplete suppression of HIV replication. The rapid replication rate of HIV and its inherent genetic variation have led to the identification of many HIV variants that exhibit altered drug susceptibility. The growing number of drug resistance mutations listed in this revised table stands as a testimony to the genetic flexibility of HIV. This table, updated in February 2007, lists 947 HIV-1 mutation/drug combinations, of which 37 occur in Gag (including this year, 3 in capsid and 3 in SP-1), 321 in Protease, 9 in Integrase, 374 in RT, and 206 in Env. Although the tables are quite comprehensive, the reader should be reminded that the HIV-1 mutations described are predominantly found in clade B virus and not in other HIV genotypes. Thirty-one mutations in HIV-2 RT and 27 in HIV-2 Protease are listed in the table. In addition, 2 mutations in SIV RT are listed.

The column "Selected or Cross-R" describes how the mutations have been identified. "Selected" refers specifically to mutations identified by *in vitro* passage of virus in increasing concentrations of a compound, or by sequencing isolates from patients on a specific drug therapy. "Cross-R" (cross-resistance) means that virus with a mutation has been shown to have decreased susceptibility to a compound even though selection of the mutation by the compound has not been reported. The "*in vitro*" column has a "Y" (for yes) when resistance or cross-resistance to the compound is seen using cloned virus or in cell culture studies; the "*in vivo*" column has a "Y" (for yes) when resistance or cross-resistance to the compound is seen in patients.

In the "Amino Acid Change" column a + means amino acids have been inserted into the sequence, while a Δ indicates a deletion. In the "Drug Class" column, "NRTI" refers to nucleoside or nucleotide reverse transcriptase inhibitors, while non-nucleoside or HIV-1 specific RT inhibitors are called "NNRTI." The abbreviation MN stands for "Multiple Nucleoside" and refers to resistance to combinations of NRTIs. "MDR" or multi-drug resistant is noted in the "Compound" column if a mutation causes resistance to multiple compounds. Other abbreviations are listed in a separate Abbreviations Table on page 137. All of the information contained in these printed tables and other useful tools are available at our Web site: `http://resdb.lanl.gov/Resist_DB`.

The authors gratefully acknowledge their colleagues for assistance in assembling this table. This work was supported in part by Los Alamos National Laboratory.

Contents

HIV-1 Gag 59
HIV-1 Capsid 61
HIV-1 SP-1 62
HIV-1 Protease 63
HIV-2 Protease 89
HIV-1 RT 91
HIV-2 RT 111
SIV RT 114
HIV-1 Integrase 115
HIV-1 Envelope 116
Table of Abbreviations 137
Table of Compounds 137
References 143

HIV-1 Gag

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
E 12 K		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
E 12 K		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
V 35 I		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02
V 35 I		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
E 40 K		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02
E 40 K		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
L 75 R		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
G 123 E		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02
G 123 E		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
Q 199 H		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
H 219 Q		Protease Inhibitor	JE-2147	Selected	Y	?		Gatanaga02
H 219 Q		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02
H 219 Q		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
H 219 Q		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
G 381 S		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02
V 390 A		Protease Inhibitor	JE-2147	Selected	Y	?		Gatanaga02
V 390 D		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
R 409 K		Protease Inhibitor	JE-2147	Selected	Y	?		Gatanaga02
R 409 K		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02
R 409 K		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
R 409 K		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
G 412 D		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
A 431 V		Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?		Gatanaga02

HIV-1 Gag

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 436 E		Protease Inhibitor	RO033–4649	Selected	Y		This PI did not select resistance in the protease gene. Sequencing showed that mutations were in the NC/p1 cleavage site.	Nijhuis07
I 437 T		Protease Inhibitor	RO033–4649	Selected	Y		This PI did not select resistance in the protease gene. Sequencing showed that mutations were in the NC/p1 cleavage site.	Nijhuis07
I 437 V		Protease Inhibitor	RO033–4649	Selected	Y		This PI did not select resistance in the protease gene. Sequencing showed that mutations were in the NC/p1 cleavage site.	Nijhuis07
L 449 F		Protease Inhibitor	JE-2147	Selected	Y	?		Gatanaga02
L 449 F		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
L 449 F		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02
E 468 K		Protease Inhibitor	UIC-94003	Selected	Y	?		Gatanaga02
E 468 K		Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?		Gatanaga02

HIV-1 CA

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
H 226 Y		Maturation inhibitor	PA-457 (Bevirimat)	Selected	Y		Mutations found near the C terminus of capsid	Adamson06
L 231 F		Maturation inhibitor	PA-457 (Bevirimat)	Selected	Y		Mutations found near the C terminus of capsid	Adamson06
L 231 M		Maturation inhibitor	PA-457 (Bevirimat)	Selected	Y		Mutations found near the C terminus of capsid	Adamson06

HIV-1 SP1

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
A 1 V		Maturation inhibitor	PA-457 (Bevirimat)	Selected	Y		Mutations found in SP-1 peptide	Adamson06
A 3 T		Maturation inhibitor	PA-457 (Bevirimat)	Selected	Y		Mutations found in SP-1 peptide	Adamson06
A 3 V		Maturation inhibitor	PA-457 (Bevirimat)	Selected	Y		Mutations found in SP-1 peptide	Adamson06

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
T 4 P	ACT→CCT	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
R 8 K	CGA→AAA	Protease Inhibitor	A-77003	Selected	Y	?	R8K/M46I/G48V: 20-fold	Ho94, Tisdale95
R 8 Q	CGA→CAA	Protease Inhibitor	A-77003	Selected	Y	?	M46I improves replication competency of R8Q mutant. Selected in chronically infected cells at 10 microM.	Ho94, Kaplan94
L 10 F	CTC→TTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	Y	In vitro, I84V/L10F/M46I: 4 fold I84V/L10F/M46I/T91S: 12 fold I84V/L10F/M46I/T91S/V32I/I47V: 46 fold Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation). In vivo, susceptibility was reduced by mutations at positions 82, 54, 10, 63, 71, 84 (4–10-fold), K20M/R (>20-fold), F53L (>40-fold)	Carrillo98, Kempf01
L 10 F	CTC→TTC	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Sequential accumulation of mutations in passage of pNL4–3 in MT4 cells in presence of a LPV/ritonavir ration of 5:1. Appears second in sequence, in passage 9, after I84V and followed by M46I, V32I, I47V, Q58E.	Mo03
L 10 F	CTC→TTC	Protease Inhibitor	ABT-538 (ritonavir)	Cross-R	Y	?	9-fold resistant to JE-2147-selected virus (L10F/M46I/I47V/I84V)	Yoshimura99
L 10 F	CTC→TTC	Protease Inhibitor	ABT-538 (ritonavir)	Cross-R	Y	?	21-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
L 10 F	CTC→TTC	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96
L 10 F	CTC→TTC	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
L 10 F	CTC→TTC	Protease Inhibitor	DMP 450	Selected	Y	?	Probably compensatory	Hodge96

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
L 10 F	CTC→TTC	Protease Inhibitor	DMP-323	Selected	Y	?	L10F/V82A: 2-fold; L10F/K45I/I84V: 50-fold	Tisdale95, King95
L 10 F	CTC→TTC	Protease Inhibitor	JE-2147	Selected	Y	?	L10F/I47V/I84V:19-fold. L10F/M46I/I47V/I84V:28-fold. >50 passages required for isolation of resistant virus.	Yoshimura99
L 10 F	CTC→TTC	Protease Inhibitor	KNI-272 (kynostatin)	Cross-R	Y	?	7-fold resistant to JE-2147 selected virus (L10F/M46I/I47V/I184V)	Yoshimura99
L 10 F	CTC→TTC	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
L 10 F	CTC→TTC	Protease Inhibitor	SC-55389A	Selected	Y	?	N88S/L10F: 25-fold	Smidt97
L 10 F	CTC→TTC	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	10-fold resistant against aprenavir-selected mutant L10F/V32I/M46I/I54M/A71V/I84V. 73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03
L 10 F	CTC→TTC	Protease Inhibitor	UIC-94003	Selected	Y	?	in vitro selection in MT-2 cells, passage 62	Gatanaga02
L 10 F	CTC→TTC	Protease Inhibitor	VB-11,328	Selected	Y	?	L10F/I84V: 8-fold	Partaledis95
L 10 F	CTC→TTC	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	Selected first	Partaledis95
L 10 I	CTC→ATC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
L 10 I	CTC→ATC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of ritonavir. Appeared late in selection (passage 44)	Watkins03
L 10 I	CTC→ATC	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Matsuoka-Aizawa03
L 10 I	CTC→ATC	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96
L 10 I	CTC→ATC	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
L 10 R	CTC→CGC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
L 10 R	CTC→CGC	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	L10R/M46I/L63P/V82T: 4-fold; L10R/M46I/ L63P/V82T/I84V: 8-fold	Condra96, Condra95
L 10 V	CTC→GTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
L 10 V	CTC→GTC	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
L 10 V	CTC→GTC	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96, Condra95
L 10 V		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
L 10 Y	CTC→TAC	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
I 11 V	ATC→GTC	Protease Inhibitor	SC-52151 (telinavir)	Selected	Y	?	I11V/M46I/F53L/A71V/N88D:10- to 20-fold	Smidt97
T 12 K	ACA→AAA	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
I 13 V	ATA→GTA	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
I 13 V	ATA→GTA	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumu-lated to give 87 fold resistance to tipranavir	Doyon05
K 14 R	AAG→AGG	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
I 15 V	ATA→GTA	Protease Inhibitor	PNU-140690 (tipranavir)	Selected	?	Y		Rusconi00

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
G 16 A	GGG→GCG	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
G 16 E	GGG→GAG	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	In vitro, Passage 17 virus I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: reduced susceptibility 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation). In vivo, susceptibility was reduced 4–10-fold in conjunction with mutations at 82, 54, 10, 63, 71, and 84; >20-fold with K20M/R and >40-fold with F53L.	Carrillo98
G 16 E	GGG→GAG	Protease Inhibitor	ABT-538 (ritonavir)	Cross-R	Y	?	21-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
G 16 E	GGG→GAG	Protease Inhibitor	Ro 31–8959 (saquinavir)	Cross-R	Y	?	4-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
K 20 I	AAG→?	Protease Inhibitor	ABT-378 (lopinavir)	Selected	?	Y		Parkin03
K 20 I	AAG→ATC	Protease inhibitor	multiple PI	Selected	?	Y		Svicher05
K 20 M	AAG→ATG	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
K 20 M	AAG→ATG	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	Seen in two patients following a switch from saquinavir. Associated with reduced suscepti-bility to both saquinavir and nelfinavir.	Lawrence99
K 20 M	AAG→ATG	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96
K 20 M		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 20 R	AAG→AGG	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
K 20 R	AAG→AGG	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	Secondary mutation occurs in combination with mutations at V82, I84, M36, I54, and A71.	Molla96
K 20 R	AAG→AGG	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96
K 20 R		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
K 20 T	AAG→ACG	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
K 20 T	AAG→ACG	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y	Associated with L90M	Svicher05
K 20 V		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
A 22 V	GCT→GTT	Protease inhibitor	multiple PI	Selected	?	Y		Svicher05
L 23 I	CTA→ATA	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96
L 23 I	CTA→ATA	Protease inhibitor	multiple PI	Selected	?	Y	Mutation selected when either nelfinavir or saquinavir used as sole PI; also selected in patients receiving ritanovir-boosted amprenavir or saquinavir	Johnston04
L 24 I	TTA→ATA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
L 24 I	TTA→ATA	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of ritonavir.	Watkins03
L 24 I	TTA→ATA	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96, Condra95

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
L 24 I	TTA→ATA	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
L 24 I	TTA→ATA	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03
D 30 N	GAT→AAT	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	D30N/A71V: 7-fold; D30N and N88D are most common in vivo after 24 weeks of therapy; they do not cause cross-resistance to other protease inhibitors	Patick98
D 30 N		Protease Inhibitor	TMC-114	Cross-R	Y		Authors use high resoultion crystallography to determine the molecular basis for inhibiton by TMC-114	Kovalevsky06
V 32 I	GTA→ATA	Protease Inhibitor	A-77003	Selected	Y	?	V32I appears first; occurs with R8Q or V82I/M46L	Kaplan94
V 32 I	GTA→ATA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	I84V/L10F/M46I/T91S/V32I/I47V: 46 fold Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation).	Carrillo98
V 32 I	GTA→ATA	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Sequential accumulation of mutations in passage of pNL4–3 in MT4 cells in presence of a LPV/ritonavir ration of 5:1. Appears fourth in sequence, in passage 11, after I84V, L10F and M46I, and followed by I47V, Q58E.	Mo03
V 32 I	GTA→ATA	Protease Inhibitor	BILA 1906 BS	Selected	Y	?	Dominant population at passage 33: V32I/M46I/A71V/I84A: 520-fold resistant. Associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′)	Croteau97
V 32 I	GTA→ATA	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 32 I	GTA→ATA	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
V 32 I	GTA→ATA	Protease Inhibitor	JE-2147	Selected	Y	?	in vitro selection in MT-2 cells, passage 33	Gatanaga02
V 32 I	GTA→ATA	Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	N	in vitro selection in MT-2 cells, passage 27	Gatanaga02, Gulnik95
V 32 I	GTA→ATA	Protease Inhibitor	MK-639 (indinavir)	Selected	Y	Y	V32I/M46L/V82A: 3-fold; V32I/M46L/A71V/V82A: 14-fold	Condra96, Condra95
V 32 I	GTA→ATA	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
V 32 I	GTA→ATA	Protease Inhibitor	Ro 31–8959 (saquinavir)	Cross-R	Y	?	4-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
V 32 I	GTA→ATA	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	10-fold resistant against aprenavir-selected mutant L10F/V32I/M46I/I54M/A71V/I84V.	Koh03
V 32 I	GTA→ATA	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	in vitro selection in MT-2 cells, passage 10	Gatanaga02
L 33 F	TTA→TTC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	Secondary mutation occurs in combination with mutations at V82, I84, M36, I54, and A71.	Molla96
L 33 F	TTA→TTC	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
L 33 F	TTA→TTT	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
L 33 I	TTA→ATA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	Associated with Clade E virus	Ariyoshi03
E 34 Q	GAA→CAA	Protease inhibitor	ABT-378 (lopinavir)	Selected	?	Y	Associated with either L33F or F53L	Svicher05
E 34 Q	GAA→CAA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	Selected by passage 24 in an In vitro passage of pNL4–3 in MT4 cells in the presence of lopinavir. Genome already had I50V, M46I, L10F and I47V from previous passages. Mutation was seen in combination with V32I, Q61H and E65Q.	Mo03
E 35 D	GAA→?	Protease Inhibitor	PNU-140690 (tipranavir)	Selected	?	Y	Seen in 60% of patients receiving tipranavir therapy.	Rusconi00

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
E 35 G	GAA→GGA	Protease inhibitor	multiple PI	Selected	?	Y		Svicher05
E 35 G		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
M 36 I	ATG→ATA	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	In vivo, V82 occurs first, often followed by changes at 54, 71 and 36	Molla96
M 36 I	ATG→ATA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	D30N/M36I/L63P: 60-fold, although L63P may be a polymorphism.	Patick98
M 36 I	ATG→ATA	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
M 36 L	ATG→CTG	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	In vivo, V82 occurs first, often followed by changes at 54, 71 and 36	Molla96
M 36 V	ATG→GTG	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
N 37 D		Protease Inhibitor	PNU-140690 (tipranavir)	Selected	?	Y	Seen in 30% of patients receiving tipranavir therapy.	Rusconi00
S 37 D	AGT→GAT	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	These non active site mutations are associated with lower binding affinity of the inhibitors to protease in enzymatic assays Protease containing these mutations were assayed: L10I/M36I/S37D/M46I/R57K/L63P/A71V/G73S/L90M/I93L	Muzammil03, Olsen99
R 41 K	AGA→AAA	Protease Inhibitor	PNU-140690 (tipranavir)	Selected	?	Y	Seen in 20% of patients receiving tipranavir therapy.	Rusconi00
R 41 T	AGA→ACA	Protease inhibitor	TMC114 (UIC-94017)	Selected	Y	?	Contrary to selection data, SDM were tested against TMC114 and susceptibility was increased	DeMeyer05
K 43 T	AAA→ACA	Protease inhibitor	ABT-378 (lopinavir)	Selected	?	Y	Associated with either I54A or with multi PI resistance mutations V82A, V32I, and I47V	Svicher05
K 43 T		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
K 45 I	AAA→ATA	Protease Inhibitor	DMP-323	Selected	Y	?	L10F/K45I/I84V: 50-fold	Tisdale95, King95
K 45 I	AAA→ATA	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
K 45 R	AAA→AGA	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y	Associated with D30N and N88D	Svicher05

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
M 46 F	ATG→TTC	Protease Inhibitor	A-77003	Selected	Y	?	Selected in chronically infected cells at 1 microM	Kaplan94
M 46 I	ATG→ATA	Protease Inhibitor	A-77003	Selected	Y	?	No effect on susceptibility but improves replication competency of R8Q mutant; R8K/M46I/G48V: 20-fold	Ho94, Kaplan94
M 46 I	ATG→ATA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	Acquired in conjunction with M46I of in vitro passage of pNL4–3 in MT4 cells, passage 7	Mo03
M 46 I	ATG→ATA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	I84V/L10F/M46I: 4 fold I84V/L10F/M46I/T91S: 12 fold I84V/L10F/M46I/T91S/V32I/I47V: 46 fold Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation).	Carrillo98
M 46 I	ATG→ATA	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Acquired in conjunction with I50V in passage 8 (pNL4–3 in MT4 cells, in 1:5 lopinavir/ritonavir)	Mo03
M 46 I	ATG→ATA	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Sequential accumulation of mutations in passage of pNL4–3 in MT4 cells in presence of a LPV/ritonavir ration of 5:1. Appears third in sequence, in passage 9 to 11, after I84V and L10F, and followed by V32I, I47V, Q58E.	Mo03
M 46 I	ATG→ATA	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	Y	In vitro, occurs after selection of I84V. In vivo, V82A/F/T/S occurs first, followed by changes at 54, 71 and 36	Markowitz95, Molla96
M 46 I	ATG→ATA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	Y	Y	5-fold resistance in combination with I84V; often seen with D30N in vivo	Patick96, Patick98
M 46 I	ATG→ATA	Protease Inhibitor	BILA 1906 BS	Selected	Y	?	Dominant population at passage 33: V32I/M46I/A71V/I84A: 520-fold resistant. Associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′)	Croteau97, Doyon96
M 46 I	ATG→ATA	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
M 46 I	ATG→ATA	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
M 46 I	ATG→ATA	Protease Inhibitor	DMP 450		Y	?	Probably compensatory	Hodge96
M 46 I	ATG→ATA	Protease Inhibitor	JE-2147	Selected	Y	?	L10F/M46I/I47V/I84V:28-fold. >50 passages required for isolation of resistant virus.	Yoshimura99
M 46 I	ATG→ATA	Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?	in vitro selection in MT-2 cells, passage 27	Gatanaga02
M 46 I	ATG→ATA	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	Condra96, Condra95
M 46 I	ATG→ATA	Protease Inhibitor	Ro 31–8959 (saquinavir)	Cross-R	Y	?	4-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
M 46 I	ATG→CTG	Protease Inhibitor	SC-52151 (telinavir)	Selected	Y	?	I11V/M46I/F53L/A71V/N88D:10- to 20-fold	Smidt97
M 46 I	ATG→ATA	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	10-fold resistant against aprenavir-selected mutant L10F/V32I/M46I/I54M/A71V/I84V. 73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03
M 46 I	ATG→ATA	Protease Inhibitor	UIC-94003	Selected	Y	?	in vitro selection in MT-2 cells, passage 62	Gatanaga02
M 46 I	ATG→ATA	Protease Inhibitor	VB-11,328	Selected	Y	?	I50V/M46I/I47V: 20-fold	Partaledis95
M 46 I	ATG→ATA	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	Arose at later passages; L10F/I84V already present	Partaledis95
M 46 L	ATG→TTC	Protease Inhibitor	A-77003	Selected	Y	?		Kaplan94
M 46 L	ATG→TTG	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
M 46 L	ATG→TTG	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of ritonavir. Appeared early in selection.	Watkins03
M 46 L	ATG→CTG	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	Y	Secondary mutation occurs in combination with mutations at V82, I84, M36, I54, and A71.	Molla96

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
M 46 L	ATG→TTG	Protease Inhibitor	BILA 1906 BS	Selected	Y	?	Dominant population at passage 33: M46L/A71V/I84A: 520-fold resistant. Associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′)	Croteau97, Doyon96
M 46 L	ATG→CTG	Protease Inhibitor	DMP-323	Selected	Y	?	V82A/M46L: 7-fold; V82A/M46L/L97V: 11-fold	King95
M 46 L	ATG→TTG	Protease Inhibitor	MK-639 (indinavir)	Selected	Y	Y	Appears second in sequence. Combination V82A/M46L/V32I/A71V: 14-fold	Tisdale95
M 46 L		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
M 46 L	ATG→TTG	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
M 46 L	ATG→TTG	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
M 46 L	ATG→CTG	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	In combination with I50V	Tisdale95
I 47 A	ATA→GCA	Protease inhibitor	ABT-378 (lopinavir)	Selected	Y	Y	Causes hypersusceptibility to saquinavir	Carillo98
I 47 A	ATA→GCA	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
I 47 V	ATA→GTA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	I84V/L10F/M46I/T91S/V32I/I47V: 46 fold Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation).	Carrillo98
I 47 V	ATA→GTA	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Sequential accumulation of mutations in passage of pNL4–3 in MT4 cells in presence of a LPV/ritonavir ration of 5:1. Appears fifth in sequence, in passage 17, after I84V, L10F, M46I and V32I, and followed by Q58E.	Mo03

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 47 V	ATA→GTA	Protease Inhibitor	ABT-538 (ritonavir)	Cross-R	Y	?	21-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
I 47 V	ATA→CTA	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96
I 47 V	ATA→CTA	Protease Inhibitor	JE-2147	Selected	Y	?	L10F/I47V/I84V:19-fold. L10F/M46I/I47V/I84V:28-fold. >50 passages required for isolation of resistant virus.	Yoshimura99
I 47 V	ATA→CTA	Protease Inhibitor	KNI-272 (kynostatin)	Cross-R	Y	?	7-fold resistant to JE-2147 selected virus (L10F/M46I/I47V/I184V)	Yoshimura99
I 47 V		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
I 47 V	ATA→GTA	Protease Inhibitor	Ro 31–8959 (saquinavir)	Cross-R	Y	?	4-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
I 47 V	ATA→CTA	Protease Inhibitor	VB-11,328	Selected	Y	?	I50V/M46I/I47V: 20-fold	Partaledis95
I 47 V	ATA→CTA	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	Arose at later passages; L10F/I84V already present	Partaledis95
G 48 M		Protease Inhibitor	P-1946	Cross-R	Y		Caused 28 fold reduced suscpetibility in conjunction with mutations at 82, 90, 53, and 54	Sevigny06
G 48 V	GGG→GTG	Protease Inhibitor	A-77003	Selected	Y	N	R8K/M46I/G48V: 20-fold; G48V/I82T: 100-fold	Borman96
G 48 V	GGG→GTG	Protease Inhibitor	MK-639 (indinavir)	Selected	?	Y		Vasudevachari96
G 48 V	GGG→GTG	Protease Inhibitor	MP-134	Cross-R	Y	?	MP-167-selected virus confers 5-fold increase in IC90	Mo96
G 48 V	GGG→GTG	Protease Inhibitor	MP-167	Selected	Y	?	L10F/G48V: 20-fold	Mo96
G 48 V	GGG→GTG	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	Y	G48V/L90M: >100-fold enzyme resistance; G48V/L90M/I54V: > 50-fold (subtype B or O). In vivo, also had V82A	Jacobsen95, Eberle95, Winters98a

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
G 48 V	GGG→GTG	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
G 48 V	GGG→GTG	Protease Inhibitor	SC-52151 (telinavir)	Cross-R	Y	?	MP-167-selected virus confers 16-fold increase in IC90	Mo96
I 50 L	ATT→CTT	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	Y		Gong00, Colonno04
I 50 L	ATT→CTT	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
I 50 V	ATT→GTT	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	Acquired in conjunction with M46I of in vitro passage of pNL4–3 in MT4 cells, passage 7	Mo03
I 50 V	ATT→GTT	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Acquired in conjunction with M46I in passage 8 (pNL4–3 in MT4 cells, in 1:5 lopinavir/ritonavir)	Mo03
I 50 V		Protease Inhibitor	TMC-114	Cross-R	Y		Authors use high resoultion crystallography to determine the molecular basis for inhibiton by TMC-115	Kovalevsky06
I 50 V	ATT→GTT	Protease Inhibitor	UIC-94003	Selected	Y	?	in vitro selection in MT-2 cells, passage 62	Gatanaga02
I 50 V	ATT→GTT	Protease Inhibitor	VB-11,328	Selected	Y	?	I50V/M46I/I47V: 20-fold	Partaledis95
I 50 V	ATT→GTT	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	Replaced I84V	Partaledis95
F 53 L	TTT→?	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
F 53 L		Protease Inhibitor	P-1946	Cross-R	Y		Caused 28 fold reduced suscpetibility in conjunction with mutations at 48,82, 90, and 54	Sevigny06
F 53 L	TTT→?	Protease Inhibitor	SC-52151 (telinavir)	Selected	Y	?	I11V/M46I/F53L/A71V/N88D:10- to 20-fold	Smidt97

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
F 53 Y	TTT→TAT	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
I 54 A	ATC→GCC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	?	Y		Parkin03
I 54 A		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
I 54 L	ATC→CTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
I 54 L	ATT→CTT	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	Y		Maguire02
I 54 M	ATC→ATG	Protease Inhibitor	ABT-378 (lopinavir)	Selected	?	Y		Parkin03
I 54 M	ATT→ATG	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96
I 54 M		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
I 54 M	ATT→ATG	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	10-fold resistant against aprenavir-selected mutant L10F/V32I/M46I/I54M/A71V/I84V.	Koh03
I 54 M	ATC→ATG	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	in vitro selection in MT-2 cells, passage 31	Gatanaga02
I 54 S	ATC→AGC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	?	Y		Parkin03
I 54 T	ATC→ACC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 54 V	ATC→GTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, suceptibility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
I 54 V	ATC→GTC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	In vivo, V82A/F/T/S occurs first, followed by changes at 54, 71 and 36	Molla96
I 54 V		Protease Inhibitor	P-1946	Cross-R	Y		Caused 28 fold reduced suscpetibility in conjunction with mutations at 48, 82, 90, 53, and 54	Sevigny06
I 54 V	ATC→GTC	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
I 54 V	ATA→GTA	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	In subtype O and B	Eberle95
I 54 V	ATA→GTA	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
K 55 R	AAA→AGA	Protease inhibitor	ABT-378 (lopinavir)	Selected	?	Y	Associated with V82A, I54V, and M46I	Svicher05
K 55 R	AAA→AGA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	Seen in one patient following a switch from saquinavir. Associated with reduced susceptibility to both saquinavir and nelfinavir.	Lawrence99
R 57 K	AGA→AAA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	Seen in one patient following a switch from saquinavir. Associated with reduced susceptibility to both saquinavir and nelfinavir.	Lawrence99
Q 58 E		Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Sequential accumulation of mutations in passage of pNL4–3 in MT4 cells in presence of a LPV/ritonavir ration of 5:1. Appears last in sequence, in passage 17, after I84V, L10F, M46I, V32I, and I47V.	Mo03
Q 58 E		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
D 60 E	GAT→GAA	Protease Inhibitor	DMP 450	Selected	Y	?	Probably compensatory	Hodge96

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
D 60 E	GAT→GAA	Protease Inhibitor	PNU-140690 (tipranavir)	Selected	?	Y	Seen in 30% of patients receiving tipranavir therapy.	Rusconi00
Q 61 H	CAG→?	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	Selected by passage 24 in an In vitro passage of pNL4–3 in MT4 cells in the presence of lopinavir. Genome already had I50V, M46I, L10F and I47V from previous passages. Mutation was seen in combination with V32I, E34Q, and E65Q.	Mo03
L 63 A	CTC→GCC	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
L 63 C	CTC→TGC	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
L 63 P	CTC→CCC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
L 63 P	CTC→CCC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of ritonavir. Appeared early in selection.	Watkins03
L 63 P	CTC→CCC	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
L 63 P	CTC→CCC	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T/I84V: 8-fold; L10R/M46I/L63P/V82T: 4-fold	Condra96, Condra95
L 63 P	CTC→CCC	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	Selected by passage 27 of in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of indinavir.	Watkins03
L 63 P	CTC→CCC	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
L 63 P	CTC→CCC	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
L 63 Q	CTC→CAG	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
L 63 S	CTC→TCC	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
L 63 T	CTC→ACC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	?	Y		Parkin03
I 64 V	ATA→GTA	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
E 65 Q	GAA→CAA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	Selected by passage 24 in an In vitro passage of pNL4–3 in MT4 cells in the presence of lopinavir. Genome already had I50V, M46I, L10F and I47V from previous passages. Mutation was seen in combination with V32I, E34Q, and Q61H.	Mo03
I 66 F	ATC→TTC	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
H 69 K		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
H 69 Y	CAT→TAT	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation).	Carrillo98
H 69 Y	CAT→TAT	Protease Inhibitor	ABT-538 (ritonavir)	Cross-R	Y	?	21-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
H 69 Y	CAT→TAT	Protease Inhibitor	Ro 31–8959 (saquinavir)	Cross-R	Y	?	4-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
K 70 E	AAA→GAA	Protease inhibitor	TMC114 (UIC-94017)	Selected	Y	?		DeMeyer05

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
A 71 I	GCT→ATT	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
A 71 L	GCT→CTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
A 71 T	GCT→ACT	Protease Inhibitor	A-77003	Cross-R	Y	?	BMS-186318-selected virus A71T/V82A: 4-fold	Patick95
A 71 T	GCT→ACT	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
A 71 T	GCT→ACT	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y		Patick98
A 71 T	GCT→ACT	Protease Inhibitor	BMS-186318	Selected	Y	?	A71T/V82A: 15-fold	Patick95
A 71 T	GCT→ACT	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96, Condra95
A 71 T	GCT→ACT	Protease Inhibitor	PNU-140690 (tipranavir)	Selected	?	Y		Rusconi00
A 71 V	GCT→GTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
A 71 V	GCT→GTT	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	Y	Occurred by passage 22 in vitro preceded by I84V, M46I and V82F. In vivo, V82A/F/T/S occurs first, followed by changes at 54, 71 and 36	Markowitz95, Molla96
A 71 V	GCT→GTT	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	D30N/A71V: 7-fold; M46I/L63P/A71V/I84V: 30-fold	Patick98

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
A 71 V	GCT→GTT	Protease Inhibitor	BILA 1906 BS	Selected	Y	?	Dominant population at passage 33: V32I/M46I/A71V/I84A or M46L/A71V/I84A: 520-fold resistant. Associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′)	Croteau97, Doyon96
A 71 V	GCT→GTT	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96
A 71 V	GCT→GTT	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
A 71 V	GCT→GTT	Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	N	in vitro selection in MT-2 cells, passage 27, in 30% of clones	Gatanaga02, Gulnik95
A 71 V	GCT→GTT	Protease Inhibitor	MK-639 (indinavir)	Selected	Y	Y	Appears fourth in sequence. Combination V82A/M46L/V32I/A71V: 14-fold	Tisdale95
A 71 V	GCT→GTT	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
A 71 V	GCT→GTT	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of saquinavir. This mutation appeared in early in passage and was maintained until the appearance of V77I.	Watkins03
A 71 V	GCT→GTT	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
A 71 V	GCT→GTT	Protease Inhibitor	SC-52151 (telinavir)	Selected	Y	?	I11V/M46I/F53L/A71V/N88D:10- to 20-fold	Smidt97
A 71 V	GCT→GTT	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	10-fold resistant against aprenavir-selected mutant L10F/V32I/M46I/I54M/A71V/I84V. 73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03
A 71 V	GCT→GTT	Protease Inhibitor	UIC-94003	Selected	Y	?	in vitro selection in MT-2 cells, passage 62	Gatanaga02

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
A 71 V	GCT→GTT	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	in vitro selection in MT-2 cells, passage 31	Gatanaga02
G 73 S	GGT→AGT	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	Seen in two patients following a switch from saquinavir. Associated with reduced susceptibility to both saquinavir and nelfinavir.	Lawrence99
G 73 S	GGT→GCT	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	Emerges following a switch from saquinavir to indinavir.	Dulioust99
G 73 S	GGT→GCT	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	Selected by passage 18 of in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of indinavir.	Watkins03
G 73 S	GGT→GCT	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
G 73 S	GGT→GCT	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03
T 74 P		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
T 74 S	ACA→TCA	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Svicher05
L 76 V	TTA→GTA	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
V 77 I	GTA→ATA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y		Patick98
V 77 I	GTA→ATA	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of saquinavir. This mutation appeared late in the passage and correlated with a reversion of A71V.	Watkins03
V 77 I	GTA→ATA	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 82 A	GTC→GCC	Protease Inhibitor	A-77003	Selected	Y	?	Rare; seen with M46F; V32I appears first; progression to V32I/M46V and V32I//M46V/A71V/V82A occurs even in the absence of drug	Borman96
V 82 A	GTC→GCC	Protease Inhibitor	A-77003	Cross-R	Y	?	BMS-186318-selected virus A71T/V82A: 4-fold	Patick95
V 82 A	GTC→GCC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
V 82 A	GTC→GCC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	In vivo, V82 occurs first, often followed by changes at I54, A71 and M36.	Molla96
V 82 A	GTC→GCC	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y		Lawrence99
V 82 A	GTC→GCC	Protease Inhibitor	BMS-186318	Selected	Y	?	A71T/V82A: 15-fold	Patick95
V 82 A	GTC→GCC	Protease Inhibitor	DMP-323	Selected	Y	?	V82A/M46L: 7-fold; V82A/M46L/L97V: 11-fold	King95
V 82 A	GTC→GCC	Protease Inhibitor	MK-639 (indinavir)	Selected	Y	Y	V32I/M46L/V82A: 3-fold; V32I/M46L/A71V/V82A: 14-fold	Condra96, Condra95
V 82 A		Protease Inhibitor	P-1946	Cross-R	Y		Caused 28 fold reduced suscpetibility in con-junction with mutations at 48, 90, 53, and 54	Sevigny06
V 82 A	GTC→GCC	Protease Inhibitor	P9941	Selected	Y	?	Used plaque assay and endpoint titration to select mutant.	Otto93
V 82 A	GTC→GCC	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	N	Y	Follows G48V during saquinavir therapy or after a switch to nelfinavir or indinavir.	Winters98a
V 82 F	GTC→TTC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
V 82 F	GTC→TTC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	Y	In vivo, V82 occurs first, often followed by changes at I54, A71 and M36. Molecular clone of V82F alone: 4–5-fold resistant in vitro.	Markowitz95, Molla96
V 82 F	GTC→TTC	Protease Inhibitor	DMP-323	Selected	Y	?	V82F/I84V: 97-fold	King95

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 82 I	GTC→ATC	Protease Inhibitor	A-77003	Selected	Y	?	No resistance alone but V32I and V82I are synergistic mutations yielding 20-fold enzyme resistance.	Kaplan94
V 82 I	GTC→ATC	Protease Inhibitor	JE-2147	Selected	Y	?	in vitro selection in MT-2 cells, passage 33	Gatanaga02
V 82 I	GTC→ATC	Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	?	in vitro selection in MT-2 cells, passage 27	Gatanaga02
V 82 L	GTC→CTC	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
V 82 L	GTC→CTC	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
V 82 M	GTC→ATG	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Resch05
V 82 S	GTC→TCC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	?	Y		Parkin03
V 82 S	GTC→TCC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	V82S or T occurs after V82A or F.	Molla96
V 82 T	GTC→ACC	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
V 82 T	GTC→ACC	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	V82S or T occurs after V82A or F.	Molla96
V 82 T	GTC→ACC	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	Condra96, Condra95
V 82 T		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06
V 82 T	GTC→ACC	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for sucepti-bility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
V 82 T	GTC→ACC	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	73-fold resistant against indinavir-selected L10F/L24I/M46I/L63P/A71V/G73S/V82T	Koh03
N 83 D		Protease Inhibitor	PNU-140690 (tipranavir)	Selected		Y		Baxter06

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 84 A	ATA→GCA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	Y	?	4-fold resistance when in combination with V32I	Patick96
I 84 A	ATA→GCA	Protease Inhibitor	BILA 1906 BS	Selected	Y	?	Dominant population at passage 33: V32I/M46I/A71V/I84A or M46L/A71V/I84A: 520-fold resistant. Associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′)	Croteau97, Doyon96
I 84 A	ATA→GCA	Protease Inhibitor	MK-639 (indinavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of indinavir. This mutation appeared in conjunction with M46I, I54V, L63P and A71V.	Watkins03
I 84 A	ATA→GCA	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
I 84 V	ATA→GTA	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	I84V/L10F/M46I: 4 fold I84V/L10F/M46I/T91S: 12 fold I84V/L10F/M46I/T91S/V32I/I47V: 46 fold Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation).	Carrillo98
I 84 V	ATA→GTA	Protease Inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	Y	?	Sequential accumulation of mutations in passage of pNL4–3 in MT4 cells in presence of a LPV/ritonavir ration of 5:1. Appears first in sequence, in passage 6, followed by L10F, M46I, V32I, I47V, Q58E.	Mo03
I 84 V	ATA→GTA	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	?	Selected in in vitro passage of NL4–3 in CEMX174 cells in increasing concentrations of ritonavir. Appeared late in selection (passage 34)	Watkins03
I 84 V	ATA→GTA	Protease Inhibitor	ABT-538 (ritonavir)	Selected	Y	Y	First mutation seen in in vitro passage. Molecular clone 8–10-fold resistant.	Markowitz95, Molla96
I 84 V	ATA→GTA	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	Y	?	M46I/L63P/A71V/I84V: 30-fold	Patick96

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 84 V	ATA→GTA	Protease Inhibitor	BILA 2185 BS	Selected	Y	?	L10F/L23I/V32I/M46I/I47V/I54M/A71V/I84V: 1,500-fold with associated Gag mutations: p1/p6 cleavage site (L to F (CTT to TTT at P1′); p7/p1 cleavage site (Q to R (CAG to CGG) at P3′, A to V (GCT to CTT) at P2′).	Croteau97, Doyon96
I 84 V	ATA→GTA	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
I 84 V	ATA→GTA	Protease Inhibitor	DMP 450	Selected	Y	?		Hodge96
I 84 V	ATA→GTA	Protease Inhibitor	DMP-323	Selected	Y	?	Occurs with K45I/L10F and V82F; Molecular clone of I84V alone: 50-fold	Tisdale95, King95
I 84 V	ATA→GTA	Protease Inhibitor	JE-2147	Selected	Y	?	L10F/I47V/I84V:19-fold. L10F/M46I/I47V/I84V:28-fold. >50 passages required for isolation of resistant virus.	Yoshimura99
I 84 V	ATA→GTA	Protease Inhibitor	KNI-272 (kynostatin)	Selected	Y	N	in vitro selection in MT-2 cells, passage 27	Gatanaga02, Gulnik95
I 84 V	ATA→GTA	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y	G48V/I84V/L90M: 30-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	Condra96, Condra95
I 84 V	ATA→GTA	Protease Inhibitor	MP-134	Selected	Y	?		Mo96
I 84 V	ATA→GTA	Protease Inhibitor	MP-167	Cross-R	Y	?	MP-134-selected virus confers 5-fold increase in IC90	Mo96
I 84 V	ATA→GTA	Protease inhibitor	PNU-140690 (tipranavir)	Selected	Y	?	After 73 passages 9 other mutations accumulated to give 87 fold resistance to tipranavir	Doyon05
I 84 V	ATA→GTA	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	In combination with G48V and L90M: 30-fold	Tisdale95
I 84 V	ATA→GTA	Protease Inhibitor	Ro 31–8959 (saquinavir) + ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	Y	?	NL4–3 passaged in CEMX174 in presence of SQV+RTV+IDV. Selected mutant had other PI mutations. Used 8-mutant clone for susceptibility assays: L10I, I54V, L63P, A71V, V82T, I84V, M90L.	Watkins03
I 84 V	ATA→GTA	Protease Inhibitor	RPI-312	Selected	Y	?		el-Farrash94
I 84 V	ATA→GTA	Protease Inhibitor	SC-52151 (telinavir)	Cross-R	Y	?	MP-134-selected virus confers 8-fold increase in IC90	Mo96
I 84 V	ATA→GTA	Protease Inhibitor	TMC114 (UIC-94017)	Cross-R	Y	?	10-fold resistant against aprenavir-selected mutant L10F/V32I/M46I/I54M/A71V/I84V.	Koh03
I 84 V	ATA→GTA	Protease Inhibitor	VB-11,328	Selected	Y	?	L10F/I84V: 8-fold	Partaledis95

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 84 V	ATA→GTA	Protease Inhibitor	VX-478 (amprenavir)	Selected	Y	?	In combination with L10F	Partaledis95
I 85 V	ATT→GTT	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Svicher05
N 88 D	AAT→GAT	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	D30N and N88D are most common in vivo after 24 weeks of therapy; they do not cause cross-resistance to other protease inhibitors.	Patick98
N 88 D	AAT→GAT	Protease Inhibitor	SC-52151 (telinavir)	Selected	Y	?	N88D compensatory, no resistance alone	Smidt97
N 88 G	AAT→GGT	Protease inhibitor	ABT-378 (lopinavir) + ABT-538 (ritonavir)	Selected	?	Y		Mo05
N 88 S	AAT→AGT	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y		Patick98
N 88 S	AAT→AGT	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
N 88 S	AAT→AGT	Protease Inhibitor	MK-639 (indinavir)	Cross-R	Y	?	SC-55389A-selected mutant confers 3-fold resistance	Smidt97
N 88 S	AAT→AGT	Protease Inhibitor	SC-55389A	Selected	Y	?	Sufficient to confer resistance alone (19-fold), but 25-fold in combination with L10F	Smidt97
L 89 M	TTG→ATG	Protease Inhibitor	BMS-232632 (atazanavir)	Selected	Y	?	V32L/L33F/M46I/A71V/I84V/N88S: 183-fold. L10Y,F/I50L/L63P/A71V/N88S: 93-fold. V32I/M46I/I84V/L89M: 96-fold.	Gong00
L 90 M	TTG→ATG	Protease Inhibitor	ABT-378 (lopinavir)	Selected	N	Y	In conjunction with other mutations, sucepti-bility to lopinavir was reduced by mutations at positions 82,54,10,63,71 and 84 by 4–10-fold, K20M/R by >20-fold and F53L by >40-fold.	Kempf01
L 90 M	TTG→ATG	Protease Inhibitor	ABT-538 (ritonavir)	Selected	N	Y	Secondary mutation occurs in combination with mutations at V82, I84, M36, I54, and A71.	Molla96
L 90 M	TTG→ATG	Protease Inhibitor	AG-1343 (nelfinavir)	Selected	N	Y	Rare in patients in Patick study; more common in Lawrence study	Patick98, Lawrence99
L 90 M	TTG→ATG	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Condra96
L 90 M		Protease Inhibitor	P-1946	Cross-R	Y		Caused 28 fold reduced suscpetibility in con-junction with mutations at 48,82, 53, and 54	Sevigny06

HIV-1 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
L 90 M	TTG→ATG	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	Y	G48V/L90M: >100-fold enzyme resistance; double mutant rare in vivo; L90M most common in vivo.	Jacobsen95, Eberle95, Winters98a
L 90 M		Protease Inhibitor	TMC-114	Cross-R	Y		Authors use high resoultion crystallography to determine the molecular basis for inhibiton by TMC-116	Kovalevsky06
T 91 S	ACT→TCT	Protease Inhibitor	ABT-378 (lopinavir)	Selected	Y	?	I84V/L10F/M46I/T91S: 12 fold I84V/L10F/M46I/T91S/V32I/I47V: 46 fold Passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y: 338 fold (in presence of p7/p1 (AN/F to VN/F) cleavage-site mutation and p1/p6 (F/L to F/F) cleavage-site mutation.	Carrillo98
T 91 S	ACT→TCT	Protease Inhibitor	ABT-538 (ritonavir)	Cross-R	Y	?	21-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
T 91 S	ACT→TCT	Protease Inhibitor	Ro 31–8959 (saquinavir)	Selected	Y	?	4-fold resisance seen with lopinavir-selected passage 17 virus: I84V/L10F/M46I/T91S/V32I/I47V/V47A/G16E/H69Y	Carrillo98
Q 92 K	CAG→AAG	Protease inhibitor	multiple PI	Selected	?	Y		Svicher05
I 93 L	ATT→CTT	Protease Inhibitor	MK-639 (indinavir)	Selected	N	Y		Muzammil03, Olsen99
C 95 F	TGC→TTC	Protease inhibitor	Ro 31–8959 (saquinavir) + MK-639 (indinavir)	Selected	?	Y	Associated with L90M and I93L	Svicher05
L 97 V	TTA→GTA	Protease Inhibitor	DMP-323	Selected	Y	?	No resistance alone;V82A/M46L/L97V: 11-fold	King95

HIV-2 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 7 N	AAA→AAT	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
V 10 I	GTC→ATC	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
V 22 I	GTT→ATT	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Damond05
A 34 E	GCA→GAA	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
A 34 S	GCA→TCA	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
I 36 V	ATT→GTT	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
L 38 F	TTG→TTT	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Damond05
I 46 T	ATT→ACT	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
I 46 V	ATT→GTT	Protease inhibitor	Ro 31–8959 (saquinavir)	Selected	?	Y		Damond05
G 48 R	GGG→CGG	Protease inhibitor	Ro 31–8959 (saquinavir)	Selected	?	Y		Damond05
I 54 L	ATC→CTC	Protease inhibitor	Ro 31–8959 (saquinavir) + MK-639 (indinavir)	Selected	?	Y		Damond05
G 55 R	GGG→CGG	Protease inhibitor	ABT-538 (ritonavir)	Selected	?	Y		Damond05
V 62 A	GTT→GCT	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Damond05
E 63 A	GAG→GCG	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
E 63 Q	GAG→CAG	Protease inhibitor	Ro 31–8959 (saquinavir)	Selected	?	Y		Damond05
T 74 N	ACA→AAT	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Damond05
T 77 I	ACT→ATT	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
G 78 E	GGA→GAA	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Damond05
T 80 Y	ACA→TAT	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
I 82 F	ATT→TTT	Protease inhibitor	ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	?	Y		Damond05
I 82 M	ATT→ATG	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
I 84 L	ATA→TTA	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
I 84 V	ATA→GTA	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05

HIV-2 Protease

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
F 85 L	TTT→TTA	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05
R 87 K	AGA→AAA	Protease inhibitor	AG-1343 (nelfinavir)	Selected	?	Y		Damond05
L 90 M	TTG→ATG	Protease inhibitor	ABT-538 (ritonavir) + MK-639 (indinavir)	Selected	?	Y		Damond05
M 95 I	ATG→ATC	Protease inhibitor	MK-639 (indinavir)	Selected	?	Y		Damond05

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 35 I		Nucleoside RT Inhibitor (NRTI)		Selected		Y	Increased NRTI susceptibility	Svicher06
T 39 A		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
M 41 L	ATG→TTG/CTG	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	?	Y	M41L/T215Y: 60–70-fold; M41L/D67N/K70R/T215Y: 180-fold.	Larder89, Larder91, Kellam92
M 41 L		RT inhibitor	VRX-329747	Selected	Y			Zhang06
M 41 L		RT inhibitor	VRX-413638	Selected	Y			Zhang06
K 43 E		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
K 43 Q		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
E 44 A	GAA→GCA	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	N	Y	Confers moderate resistance in absence of M184V. Development of mutation may be promoted by thymidine analogs.	Montes02
E 44 D	GAA→GAC	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	N	Y	Confers moderate levels of resistance to 3TC (7–32-fold) when present in an AZT-resistant genetic background (41L/67N/210W/215Y)	Hertogs00
I 50 V		Nucleoside RT Inhibitor (NRTI)		Selected		Y	Increased NRTI susceptibility	Svicher06
P 52 R	CCT→CGT	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Selected	Y	?	Selection of resistant HIV-1EVK passaged in MT-4 cells	Gashnikova03
N 54 D	AAT→GAT	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Selected	Y	?	Selection of resistant HIV-1EVK passaged in MT-4 cells	Gashnikova03
A 62 T		RT inhibitor	VRX-329747	Selected	Y			Zhang06
A 62 T		RT inhibitor	VRX-413638	Selected	Y			Zhang06
A 62 V	GCC→GTC	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y	A62V alone has no effect, but in combination with mutations at 75, 77, 116, 151 causes multi NRTI resistance.	Shirasaka95
A 62 V		RT inhibitor	VRX-329747	Selected	Y			Zhang06
A 62 V		RT inhibitor	VRX-413638	Selected	Y			Zhang06
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	1592U89 (abacavir)	Selected	Y	N	K65R/L74V: 3.6-fold; K65R/M184V: 7-fold; K65R/L74V/M184V: 10.2-fold	Tisdale97
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	Y	?	>3-fold resistance	Bazmi00
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	BCH-10652 (+/- dOTC)	Selected	Y	?	K65R/M184V: 4.2-fold.	Taylor00
K 65 R	AAA→AGA	NRTI	cyclo-d4G	Cross-R	Y	?	4 fold resistance	Ray05
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	d-d4FC (D4FC)	Selected	Y	?	In vitro selection	Geleziunas03
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Selected	Y	?	Selected in 7 viruses (from patient isolates or HXB2) through in vitro selection.	Garcia-Lerma03
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Cross-R	Y	?	>3-fold resistance	Bazmi00

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Selected	Y	Y	4–10-fold resistance	Zhang94, Gu94
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Selected	N	Y	Infrequently observed in patients receiving ddI or ddC	Zhang94
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	DXG	Selected	Y	?	8.7-fold resistance	Bazmi00
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	PMEA (adefovir)	Selected	Y	N	10–25-fold resistant	Foli96
K 65 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	PMPA (tenofovir)	Selected	Y	?	3.5-fold resistant	Wainberg99
D 67 A	GAC→GCC	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	?	Selection of resistant HIV-1EVK passaged in MT-4 cells	Gashnikova03
D 67 del	GAC→deletion	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + ddI (didanosine)	Selected	N	Y	Selected by AZT + ddI. Little effect alone (1.2-fold), but 1813-fold in combination with K103N, L74I, T69G, K70R, T215Yand K219Q	Imamichi00
D 67 del	GAC→deletion	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Cross-R	N	Y	Selected by AZT+ddI in patient. Site-directed mutant: 18-fold.	Imamichi00
D 67 del	GAC→deletion	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Selected	N	Y	Selected by AZT+ddI in patient. Site-directed mutant: 3.8-fold.	Imamichi00
D 67 del	GAC→del	Nucleoside RT Inhibitor (NRTI)	MDR (multi-drug resistant)	Selected	?	Y	3 nucleotide deletion in multi-treated HIV-1 infected patient	Masciari02
D 67 E	GAC→GAG	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
D 67 G	GAC→GAG	Nucleoside RT Inhibitor (NRTI)	(+)dOTFC	Selected	Y	?		Richard00
D 67 G	GAC→GAG	Nucleoside RT Inhibitor (NRTI)	(+)dOTFC	Cross-R	Y	?		Richard00
D 67 G	GAC→GGC	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
D 67 N	GAC→AAC	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	Y	D67N/K70R/T215Y/K219Q: 120-fold; M41L/ D67N/K70R/T215Y: 180-fold.	Larder89, Larder91, Kellam92
D 67 S	GAC→?	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 G	AGT→GGT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Frequently associated with other multi-ddN resistance mutations V75I, F77L, F116Y and Q151M.	Schmit98
S 68 N	AGT→AAT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 N	AGT→AAT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 N		RT inhibitor	VRX-329747	Selected	Y			Zhang06
S 68 N		RT inhibitor	VRX-413638	Selected	Y			Zhang06

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
S 68 S + GGG	AGT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 S + SS	AGT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y	>2500-fold-R to AZT when in combination with 210W, 215Y, 62V	Larder99
S 68 S + SSG	AGT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 S + ST	AGT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 S + SV	AGT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
S 68 Y	AGT→TAT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
ins 69 TRVMG	ACT+→ACG AGA GTG ATG GGG	Nucleoside RT Inhibitor (NRTI)	1592U89 (abacavir)	Cross-R	Y	Y	32-fold resistance; duplication of 15 mutations of HIV-1 env	Lobato02
ins 69 TRVMG	ACT+→ACG AGA GTG ATG GGG	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	Y	Y	84-fold resistance; duplication of 15 mutations of HIV-1 env	Lobato02
ins 69 TRVMG	ACT+→ACG AGA GTG ATG GGG	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Cross-R	Y	Y	371-fold resistance; duplication of 15 mutations of HIV-1 env	Lobato02
ins 69 TRVMG	ACT+→ACG AGA GTG ATG GGG	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Cross-R	Y	Y	15-fold resistance; duplication of 15 mutations of HIV-1 env	Lobato02
ins 69 TRVMG	ACT+→ACG AGA GTG ATG GGG	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Cross-R	Y	Y	4-fold resistance; duplication of 15 mutations of HIV-1 env	Lobato02
ins 69 TRVMG	ACT+→ACG AGA GTG ATG GGG	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Cross-R	Y	Y	12-fold resistance; duplication of 15 mutations of HIV-1 env	Lobato02
INS 69 TSG	ACT→ins	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + ddI (didanosine) or ddC (zalcitabine)	Selected	Y	Y	Highly resistant to 3TC, ABC, d4T	Bulgheroni04
T 69 A	ACT→GCT	Multiple Nucleoside	3TC (lamivudine) + d4T (stavudine)	Selected	?	Y	Seen in one patient on 3TC + d4T combination therapy.	Lawrence99
T 69 A + SG	ACT→GCT + AGT GGT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 D	ACT→GAT	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine)	Selected	?	Y	Seen in one patient on AZT + 3TC combination therapy.	Lawrence99
T 69 D	ACT→GAT	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Selected	N	Y	5-fold resistance	Fitzgibbon92

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
T 69 G	ACT→GGT	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + ddI (didanosine)	Selected	N	Y	Selected by AZT + ddI. Little effect alone (1.5-fold), but 1813-fold in combination with K103N, L74I, T69G, K70R, T215Yand K219Q	Imamichi00
T 69 G	ACT→GGT	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Cross-R	N	Y	Selected by AZT+ddI in patient. Site-directed mutant: 11-fold.	Imamichi00
T 69 G	ACT→GGT	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Selected	N	Y	Selected by AZT+ddI in patient. Site-directed mutant: 10-fold.	Imamichi00
T 69 N	ACT→AAT	Multiple Nucleoside	3TC (lamivudine) + d4T (stavudine)	Selected	?	Y	Seen in two patients on 3TC + d4T combination therapy.	Lawrence99
T 69 S + AG	ACT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
T 69 S + EA	ACT→AGT + AGA GCA	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + EE	ACT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
T 69 S + RA	ACT→AGT + AGA GCA	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + SA	ACT→AGC + AGC GCT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + SA	ACT→TCT + AGT GCT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + SA	ACT→AGT + AGC GCT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + SG	ACT→AGT + AGT GGT	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine) + hydroxyurea	Selected	?	Y	Seen in one patient.	DeAntoni97
T 69 S + SG	ACT→AGT + AGT GGT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + SS	ACT→AGT + AGT AGT	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine) + hydroxyurea	Selected	?	Y	Seen in one patient.	DeAntoni97

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
T 69 S + SS	ACT→TCT + AGC TCT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + SS	ACT→TCT + AGT TCT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + TG	ACT→TCT + ACC GGT	Multiple Nucleoside	MDR (multi drug resistant)	Selected	?	Y		Bulgheroni04
T 69 S + TS	ACT→TCT + ACC TCT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	?	Y	Seen in heavily treated patients. Confers >4-fold resistance to: AZT, ddI, ddC, 3TC and PMEA.	Winters98
T 69 S + VG	ACT→ins	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y		Larder99
K 70 E	AAA→GAA	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	Y	?	PMEA-selected virus confers 7-fold resistance.	Cherrington96
K 70 E	AAA→GAA	Nucleoside RT Inhibitor (NRTI)	PMEA (adefovir)	Selected	Y	Y	9-fold in vitro. Also seen in patients on PMEA therapy.	Cherrington96, Miller98
K 70 R	AAA→AGA	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	Y	D67N/K70R/T215Y/K219Q: 120-fold	Larder89, Larder91, Kellam92
K 70 S	AAA→AGA	Multiple Nucleoside	ddI (didanosine) + d4T (stavudine)	Selected	?	Y	Seen in one patient on ddC + d4T combination therapy.	Lawrence99
L 74 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?		Kleim96
L 74 V	TTA→GTA	Nucleoside RT Inhibitor (NRTI)	1592U89 (abacavir)	Selected	Y	N	K65R/L74V: 3.6-fold; K65R/L74V/M184V: 10.2-fold	Tisdale97
L 74 V	TTA→GTA	NRTI	cyclo-d4G	Cross-R	Y	?	2 fold resistance	Ray05
L 74 V	TTA→GTA	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Cross-R	N	Y	5–10-fold resistant to ddI-selected virus	StClair91
L 74 V	TTA→GTA	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Selected	N	Y	Can reverse effect of T215Y AZT resistance mutation	StClair91
L 74 V	TTA→GTA	Nucleoside RT Inhibitor (NRTI)	DXG	Selected	Y	?	4-fold resistance	Bazmi00
L 74 V	TTA→GTA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?		Kleim96
V 75 I	GTA→ATA	Nucleoside RT Inhibitor (NRTI)	(-)dOTC	Selected	Y	?	1.6-fold after 12 passages, but seen in 5 different clones	Richard99
V 75 I	GTA→TTA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?	Compensates for negative effect of G190E mutation on RT activity	Kleim96

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 75 I	GTA→ATA	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y	V75I alone has no effect, but in combination with mutations at 62, 77, 116, 151 causes multi NRTI resistance.	Shirasaka95
V 75 L	GTA→TTA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?		Kleim96
V 75 M	GTA→ATG	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Selected	N	Y	Associated with Clade E virus	Ariyoshi03
V 75 M	GTA→ATG	Multiple Nucleoside	ddC (zalcitabine) + d4T (stavudine)	Selected	?	Y	Seen in one patient on ddC + d4T combination therapy.	Lawrence99
V 75 T	GTA→ACA	Nucleoside RT Inhibitor (NRTI)	d4C	Cross-R	Y	N	d4T-selected	Lacey94
V 75 T	GTA→ACA	Nucleoside RT Inhibitor (NRTI)	d4T (stavudine)	Selected	Y	N	Observed with d4T selection in vitro, rarely in patients receiving d4T	Lacey94, Lin99
V 75 T	GTA→ACA	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Cross-R	Y	N	d4T-selected	Lacey94
V 75 T	GTA→ACA	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Cross-R	Y	N	d4T-selected	Lacey94
V 75 T	GTA→ACA	Nucleoside RT Inhibitor (NRTI)	(-)-FTC (emtricitabine)	Cross-R	Y	N	d4T-selected	Lacey94
F 77 L	TTC→CTC	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y	F77L alone has no effect, but in combination with mutations at 62, 75, 116, 151 causes multi NRTI resistance.	Shirasaka95
R 83 K		Nucleoside RT Inhibitor (NRTI)		Selected		Y	Increased NRTI susceptibility	Svicher06
W 88 G	TGG→GGG	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	N	Y	Observed after selection with AZT and PFA; suppresses effects of AZT mutations	Mellors95
W 88 S	TGG→TCG	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	N	Y	Partially suppresses effects of AZT resistance mutations	Mellors95
E 89 G	GAA→GGA	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Cross-R	Y	N	Isolated by screening RT clones for ddGTP resistance	Prasad91
E 89 K	GAA→GGA	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	Y	N	Suppresses effects of AZT resistance mutations	Tachedjian95
L 92 I	TTA→ATA	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	Y	N	Partially suppresses effects of AZT resistance mutations	Tachedjian95
A 98 G	GCA→GGA	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	N	Y		Byrnes93
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-88204E	Selected	Y	?		Balzarini93d, Vasudevachari92
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	N	Y		Richman93
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	Y	Y	Combinations of mutations needed for high-level resistance; L100I/V108I: 1,000-fold; L100I/V179D/Y181C: 1,000-fold	Young95, Winslow96, Bacheler00
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	Y	N	Not in patients	Byrnes93
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82150	Selected	Y	?	Suppresses effects of AZT resistance mutations	Mellors93, Balzarini93c
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	Y	?	Found in combination with E138K	Larder92

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-68	Selected	Y	?	70-fold resistance	Balzarini95
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-70	Selected	Y	?	Passage 6: 758-fold	Buckheit95a
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-781	Selected	Y	?	Activity of UC-781 versus L100I, K103N, V106A, E138K, Y181C and Y188L reduced by 2-, 7-, 1.5-, 1.5-, 5- and 150-fold, respectively, compared to wild type	Balzarini96a, Balzarini96b
L 100 I	TTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-84	Selected	Y	?	Passage 6: >333-fold	Buckheit95a
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	>30-fold resistant against a virus isolate, but not resistant against a site-directed mutant.	Cushman98
K 101 E	AAA→GAA	Multiple Nucleoside	AZT (zidovudine) + BHAP U-87201E (atevirdine)	Selected	?	Y	Seen in one patient on atevirdine + AZT combination therapy. Found in association with K103N.	Demeter98
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	?	15-fold to UC-781-selected virus	Buckheit97
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	Y	Y	17-fold increase in IC90	Young95, Bacheler00
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	N	Y		Byrnes93
K 101 E	AAA→GAA	noncompetitive RT inhibitor	MSK-076	Selected	Y	?	HIV-1	Auwerx04
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-10	Selected	Y	?	Found in combination, K101E/Y181C: 200-fold	Buckheit95a
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-38	Selected	Y	N	Selected In combination with G190E: > 100-fold	Balzarini95
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-57	Selected	Y	?	Selected in combination, K101E/Y181C: 58-fold	Buckheit95a
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-781	Selected	Y	?	By passage 15: Y181C/V108I/K101E: >500-fold	Buckheit97
K 101 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	UCO40	Cross-R	Y	?	18-fold to UC-781-selected virus	Buckheit97
K 101 I	AAA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-16	Selected	Y	N	Selected in combination with G141E: 10-fold	Balzarini95
K 101 P	AAA→CCA	HIV-1 Specific RT Inhibitor (NNRTI)	TMC125	Cross-R	Y	Y	Clinical isolate with this mutation is associated with decreased phenotypic susceptibility	Vingerhoets04
K 101 Q	AAA→CAA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	N	Y		Bacheler00
K 101 Q	AAA→CAA	HIV-1 Specific RT Inhibitor (NNRTI)	LY-300046 HCl (trovirdine)	Selected	Y	?	Found in combination with V108I	Zhang95, Vrang93

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 103 E	AAA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-87201E (atevirdine)	Selected	?	Y	Found in association with Y181C in one patient on monotherapy. K103E, K103N and Y181C observed with monotherapy.	Demeter98
K 103 H	AAA→CAC	NNRTI	NNRTI	Selected	?	Y		
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	>28-fold. Tested against a site-directed mutant.	Cushman98
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-87201E (atevirdine)	Selected	?	Y	Found in association with Y181C in several patients on monotherapy. Also seen in patients on ATV + AZT combination therapy.	Demeter98
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	N	Y		Richman94
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	Y	Y		Young95, Bacheler00
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	?	Y	?	Predominant mutation in vivo	Seki95
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,593	Selected	Y	?	K103N/Y181C: > 1,000-fold	Nunberg91
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	Y	Y	K103N and Y181C most common with monotherapy	Byrnes93, Saag93
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	Y	?	>100-fold alone. K103N/Y181C: > 1,000-fold	Balzarini93d
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	UC-10	Selected	Y	N	5-fold resistance	Balzarini95
K 103 N	AAA→AAC	HIV-1 Specific RT Inhibitor (NNRTI)	UC-81	Selected	Y	?		Balzarini95
K 103 Q	AAA→CAA	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	N	Y		Saag93
K 103 R	AAA→AGA	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	?	Y	Y		BorrotoEsoda97
K 103 R	AAA→AGA	HIV-1 Specific RT Inhibitor (NNRTI)	LY-300046 HCl (trovirdine)	Selected	Y	?	K103R/V179D: 500-fold; Found in combination with V179D or Y181C	Zhang95, Vrang93
K 103 R	AAA→AGA	HIV-1 Specific RT Inhibitor (NNRTI)	O-(2-Phenoxy ethyl)benzoyl (phenyl) thiocarbamate 17c	Cross-R	Y	?	Low potency also against K103N/Y181C	Ranise03
K 103 S	AAA→AGT	NNRTI	NNRTI	Selected	?	Y	clinical isolates as well as site-directed mutants tested in vitro	Harrigan05
K 103 T	AAA→ACA	NNRTI	NNRTI	Selected	?	Y		
K 103 T	AAA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	S-1153	Selected	Y	?		Fujiwara98
K 103 T	AAA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-42	Selected	Y	N	100-fold resistance	Balzarini95
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	7.13-fold. Tested against a site-directed mutant.	Cushman98
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-88204E	Selected	Y	?		Vasudevachari92
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	Y	Y		Larder92, Richman94

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	E-EBU-dM	Selected	Y	?		Balzarini93
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	S-1153	Selected	Y	?	V106A + F227L: 387-fold	Fujiwara98
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	S-2720 (quinoxaline)	Selected	Y	?	P225H follows V106A. Also seen with L101I and Y181C. Double and triple mutants highly resistant to other NNRTI's, including MKC442	Pelemans97
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	Y	?		Larder92
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-69	Selected	Y	?	Selected in combination, V106A/V181C: 166-fold	Buckheit95a
V 106 A	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-82	Selected	Y	?	Activity of UC-82 versus L100I, K103N, V106A, E138K, Y181C and Y188L reduced by 2-, 6-, 1.5-, 2-, 4- and 200-fold, respectively, compared to wild type	Balzarini96b, Balzarini96a
V 106 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?	Appears under lowered drug concentration selection	Kleim97
V 106 I		NNRTI	VRX-480773	Selected	Y			Zhang06b
V 106 M	GTG→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Cross-R	Y			Brenner03
V 106 M	GTG→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y			Brenner03
V 106 M	GTG→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	Y	Y	selected in vitro under efavirenz pressure in Clade C virus. Also developed in 3/6 efavirenz-treated patients with Clade C infection.	Brenner03
V 108 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	6.74-fold. Tested against a site-directed mutant.	Cushman98
V 108 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	N	Y		Richman94
V 108 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)		Y	?	L100I/V108I: 1,000-fold. Observed frequently in patients.	Winslow96, Bacheler00
V 108 I	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	?Selected	Y	?		Seki95
V 108 I	GTA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	Y	Y		Byrnes93
V 108 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	LY-300046 HCl (trovirdine)	Selected	Y	?	Found in combination with K101Q	Zhang95, Vrang93
V 108 I	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	N	Y	>100-fold	Vandamme94a
V 108 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-781	Selected	Y	?	By passage 10: 55-fold-R, in combination with Y181C	Buckheit97

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
G 112 S		RT inhibitor	VRX-329747	Selected	Y			Zhang06
G 112 S		RT inhibitor	VRX-413638	Selected	Y			Zhang06
Y 115 F	TAT→TTT	Nucleoside RT Inhibitor (NRTI)	1592U89 (abacavir)	Selected	Y	N	K65R/L74V and/or Y115F with M184V: 10 fold; L74V/Y115F/M184V: 11-fold	Tisdale97
F 116 Y	TTT→TAT	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y	F116Y alone has no effect, but in combination with mutations at 62, 75, 77, 151 causes multi NRTI resistance.	Shirasaka95
V 118 I	GTT→ATT	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	N	Y	Confers moderate levels of resistance to 3TC (7–32-fold) when present in an AZT-resistant genetic background (41L/67N/210W/215Y)	Hertogs00
V 118 I		RT inhibitor	VRX-329747	Selected	Y			Zhang06
V 118 I		RT inhibitor	VRX-413638	Selected	Y			Zhang06
P 119 S	CCC→TCC	NRTI	4'-Ed4T	Selected	Y	?	selected along with T165A and M184V	Nitanda05
P 119 S	CCC→TCC	Nucleoside RT Inhibitor (NRTI)	F-ddA (lodenosine)	Selected	Y	?	Found with V179D and/or L214F, which are possibly compensatory	Tanaka97
K 122 E		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
D 123 G		NNRTI	VRX-480774	Selected	Y			Zhang06b
I 135 L	ATA→AAA	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135L/L283I: 5.0-fold resistance.	Brown00
I 135 L	ATA→AAA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135L/L283I: 4.2-fold resistance.	Brown00
I 135 L	ATA→AAA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135L/L283I: 4.1-fold resistance.	Brown00
I 135 M	ATA→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135M/L283I: 4.0-fold resistance.	Brown00
I 135 M	ATA→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135M/L283I: 4.5-fold resistance.	Brown00
I 135 M	ATA→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135M/L283I: 3.2-fold resistance.	Brown00

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 135 T	ATA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135T/L283I: 2.8-fold resistance.	Brown00
I 135 T	ATA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135T/L283I: 3.4-fold resistance.	Brown00
I 135 T	ATA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. I135T/L283I: 2.5-fold resistance.	Brown00
E 138 A	GAG→GCG	HIV-1 Specific RT Inhibitor (NNRTI)	TSAO	Selected	N	Y	Mutation reducing susceptibility to TSAO in TSAO therapy naive patients.	VanLaethem00
E 138 K	GAG→AAG	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	Selected	Y	N	Obtained in the concomitant presence of low 3TC concentrations	Balzarini96c
E 138 K	GAG→AAG	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	Y	?	Found in combination with L100I	Balzarini93c
E 138 K	GAG→AAG	HIV-1 Specific RT Inhibitor (NNRTI)	TSAO	Selected	Y	?	E138A (GAG to GCG) in TSAO-naive patients confers TSAO viral resistance	Balzarini93a, Balzarini93b
E 138 K	GAG→AAG	HIV-1 Specific RT Inhibitor (NNRTI)	UC-82	Selected	Y	?	Activity of UC-82 versus L100I, K103N, V106A, E138K, Y181C and Y188L reduced by 2-, 6-, 1.5-, 2-, 4- and 200-fold, respectively, compared to wild type	Balzarini96b, Balzarini96a
E 138 K	GAG→AAG	HIV-1 Specific RT Inhibitor (NNRTI)	UC-84	Selected	Y	?		Balzarini95
T 139 I	ACA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	38-fold resistant against a virus isolate, but not tested against a site-directed mutant.	Cushman98
T 139 I	ACA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	Calanolide A	Selected	Y	?	>70-fold resistance but not cross-resistant to other NNRTIs	Buckheit95c
G 141 E	GGG→GAG	HIV-1 Specific RT Inhibitor (NNRTI)	UC-16	Selected	Y	N	Selected in combination with K101I: 10-fold	Balzarini95
P 143 S		Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Selected	Y	?	Selection of resistant HIV-1EVK passaged in MT-4 cells	Gashnikova03
Q 145 L	CAG→TTG	NRTI/NNRTI	multi-nucleoside	Cross-R	Y	Y	Resistance levels similar to Q145M	Paolucci04
Q 145 M	CAG→ATG	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	Y	Y	confers multi drug resistance to both NRTI and NNRTI; mutation selected in patient on multidrug therapy	Paolucci03
Q 151 M	CAG→ATG	Nucleoside RT Inhibitor (NRTI)	d-d4FC (D4FC)	Selected	?	Y		Geleziunas03

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Q 151 M	CAG→ATG	Multiple Nucleoside	MDR (multi-drug resistant)	Selected	N	Y	Pivotal multi nucleoside RTI resistance mutation (first to occur), found in association with combinations of four other mutations: A62V/V75I/F77L/F116Y/Q151M: AZT >190-fold; ddI 50-fold; ddC 20-fold; d4T > 10-fold	Shirasaka95
S 156 A	TCA→GCA	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	Y	N		Tachedjian95
P 157 S	CCA→TCA	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Cross-R	Y	N	Found from selection experiments with FIV (P156S); made mutant of corresponding change in HIV.	Smith99
Q 161 L	CAA→CTA	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	Y	Y	5-fold alone; Q161L/H208Y: 9-fold; suppresses effects of AZT mutations	Mellors95
T 165 A	ACA→GCA	NRTI	4'-Ed4T	Selected	Y	?	selected along with P119S and M184V	Nitanda05
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	8-chloro-TIBO (tivirapine)	Selected	Y	?	Tested against QM96521-selected virus. 10-fold.	Witvrouw98
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	28-fold. Tested against a site-directed mutant.	Cushman98
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	Y	?	11-fold alone; L100I/V179D/Y181C: 1,000-fold	Winslow96
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	N	Y		Byrnes93
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	LY-300046 HCl (trovirdine)	Selected	Y	?	Found in combination with K103R or Y181C; V179D/Y181C: > 1,000-fold	Zhang95, Vrang93
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	QM96521	Selected	Y	?	10-fold resistant. Other TTD-derivatives are 15–140 fold-R.	Witvrouw98
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	N	Y	20-fold	Vandamme94
V 179 D	GTT→GAT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-10	Selected	Y	?		Balzarini96a
V 179 E	GTT→GAG	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	N	Y		Byrnes93
V 179 F	GTT→TTT	HIV-1 Specific RT Inhibitor (NNRTI)	TMC125	Cross-R	Y	Y	Fold-change tested using double mutant V179F+Y181C	Vingerhoets04
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	1737	Selected	Y	?	Y181C also confers resistance to numerous other tetrahydronaphthalene derivatives.	Hara97
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	>28-fold. Tested against a site-directed mutant.	Cushman98
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	α-APA (loviride)	Selected	?	Y		Staszewski96
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-87201E (atevirdine)	Selected	?	Y	K103E, K103N and Y181C observed with monotherapy	Demeter98

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-88204E	Selected	Y	?		Vasudevachari92
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	Y	Y		Richman94, Richman91, Mellors92
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	BM+51.0836	Selected	Y	?		Maass93
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	Y	?	L100I/V179D/Y181C: 1,000-fold; uncommon in vivo	Winslow96
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	E-BPTU	Selected	Y	?	160-fold resistant	Buckheit95c
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	E-EBU	Selected	Y	?		Balzarini93
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	E-EPSeU	Selected	Y	?	Y188C confers greater resistance (>250-fold) than Y181C (>50-fold)	Nguyen94
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	E-EPU	Selected	Y	?	Y188C (>250-fold)confers greater resistance than Y181C (>95-fold)	Nguyen94
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	?	?	Y		BorrotoEsoda97
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,593	Selected	Y	?	K103N/Y181C: > 1,000-fold	Nunberg91
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	L-697,661	Selected	Y	Y	K103N and Y181C most common with monotherapy	Byrnes93, Saag93
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	LY-300046 HCl (trovirdine)	Selected	Y	?	V179D/Y181C: > 1,000-fold; Found in combination with K103R or V179D	Zhang95, Vrang93
Y 181 C	TAT→TGT	noncompetitive RT inhibitor	MSK-076	Selected	Y	?		Auwerx04
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	O-(2-Phenoxy ethyl)benzoyl (phenyl) thiocarbamate 17c	Cross-R	Y	?	Low potency also against K103N/Y181C	Ranise03
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	Y	?	K103N/Y181C: > 1,000-fold	Larder92
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-10	Selected	Y	?	Found in combination, K101E/Y181C: 200-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-32	Selected	Y	?	Passage 6: 38-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-38	Selected	Y	?	By passage 6: 8–149-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-57	Selected	Y	?	Selected in combination, K101E/Y181C: 58-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-581	Selected	Y	?	Passage 6: 53-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-68	Selected	Y	?	Passage 6: 5-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-69	Selected	Y	?	Selected in combination, V106A/V181C: 166-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-781	Selected	Y	?	By passage 5: 50-fold-R	Buckheit97
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-80 (NSC 639475)	Selected	Y	?	Passage 6: 18-fold	Buckheit95a
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-81	Cross-R	Y	?		Balzarini95

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Y 181 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-84	Selected	Y	?	Passage 5: >118-fold	Buckheit95a
Y 181 C		NNRTI	VRX-480773	Selected	Y			Zhang06b
Y 181 I	TGT→ATT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-88204E	Selected	Y	Y	Appeared after treatment of Y181C-mutated virus with BHAP; high-level resistance to BHAP, nevirapine and TIBO; observed in one nevirapine-treated patient	Balzarini94
Y 181 I	TGT→ATT	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	N	Y	Observed in one patient	Shaw94
Y 181 I	TAT→ATT	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	Selected	Y	N		Balzarini96c
Y 181 I	TAT→ATT	HIV-1 Specific RT Inhibitor (NNRTI)	TMC125	Cross-R	Y	Y	Clinical isolate with this mutation is associated with decreased phenotypic susceptibility	Vingerhoets04
Y 181 V	TAT→GTT	HIV-1 Specific RT Inhibitor (NNRTI)	TMC125	Cross-R	Y	Y		Vingerhoets04
M 184 I	ATG→ATA	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Selected	Y	Y	M184V and M184I can suppress effects of AZT resistance mutations	Schinazi93, Tisdale93, Gao93
M 184 I	ATG→ATA	Nucleoside RT Inhibitor (NRTI)	(+)dOTC	Selected	Y	?	Selected in <10 passages	Taylor00
M 184 I	ATG→ATA	Nucleoside RT Inhibitor (NRTI)	(+)dOTFC	Cross-R	Y	?		Richard00
M 184 I	ATG→ATA	Nucleoside RT Inhibitor (NRTI)	(-)dOTFC	Cross-R	Y	?		Richard00
M 184 I	ATG→ATA	Nucleoside RT Inhibitor (NRTI)	(-)-FTC (emtricitabine)	Selected	Y	?		Schinazi93
M 184 I	ATG→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	QYL-609	Cross-R	Y	?	QYL-selected virus.	Yoshimura99a
M 184 I	ATG→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	QYL-685	Selected	Y	?	9-fold. Additional passage of virus did not select M184V	Yoshimura99a
M 184 I	ATG→ATG	HIV-1 Specific RT Inhibitor (NNRTI)	QYL-685	Cross-R	Y	?	Additional passage of virus did not select M184V, but infectious clone was resistant.	Yoshimura99a
M 184 T	ATG→ACG	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Selected	Y	Y	Reduced replication capacity and RT activity	Keulen97, Larder95
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	1592U89 (abacavir)	Selected	Y	N	K65R/L74V and/or Y115F with M184V: 10-fold; K65R/M184V: 8-fold; L74V/M184V: 9-fold; L74V/Y115F/M184V: 11-fold	Tisdale97
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Selected	Y	Y	M184V and M184I can suppress effects of AZT resistance mutations; GTA seen in cell culture	Schinazi93, Tisdale93, Gao93
M 184 V	ATG→GTG	NRTI	4'-Ed4T	Selected	Y	?	selected at day 26 while P119S and T165A added at day 81	Nitanda05
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	BCH-10652 (+/- dOTC)	Selected	Y	?	K65R/M184V: 4.2-fold.	Taylor00
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	ddC (zalcitabine)	Cross-R	Y	Y		Gu92

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	ddI (didanosine)	Selected	Y	Y	2–5-fold resistance; Rarely observed in patients receiving ddI	Gu92, Gao92
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	(-)dOTC	Selected	Y	?	Selected in 15–20 passages	Taylor00
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	(+)dOTC	Selected	Y	?	6–7-fold resistance	Richard99
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	(-)dOTFC	Selected	Y	?	high level resistance	Richard00
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	(+)dOTFC	Cross-R	Y	?	high level resistance	Richard00
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	(-)-FTC (emtricitabine)	Selected	Y	Y	>100-fold resistance. M184V can suppress effects of AZT mutations	Schinazi93, Tisdale93
M 184 V	ATG→GTG	Nucleoside RT Inhibitor (NRTI)	L-FddC	Cross-R	Y	?	>100-fold resistant to 3TC-resistant virus	Gosselin94
M 184 V		RT inhibitor	VRX-329747	Selected	Y			Zhang06
M 184 V		RT inhibitor	VRX-413638	Selected	Y			Zhang06
Y 188 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	6.07-fold. Tested against a site-directed mutant.	Cushman98
Y 188 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	N	Y		Richman94
Y 188 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	E-EPSeU	Selected	Y	?	Y188C is the predominant mutation for E-EPSeU; Y188C confers greater resistance than Y181C	Nguyen94
Y 188 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	E-EPU	Selected	Y	?	Y188C confers greater resistance than Y181C	Nguyen94
Y 188 C	TAT→TGT	HIV-1 Specific RT Inhibitor (NNRTI)	HEPT	Selected	Y	?		Balzarini93
Y 188 H	TAT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	ADAMII	Cross-R	Y	?	>128-fold resistant against a virus isolate, but not tested against a site-directed mutant.	Cushman98
Y 188 H	TAT→CAT	Multiple Nucleoside	AZT (zidovudine) + BHAP U-87201E (atevirdine)	Selected	?	Y	Found in two patients on atevirdine + AZT combination therapy.	Demeter98
Y 188 H	TAT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	N	Y		Bacheler00
Y 188 H	TAT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	Y	?		Balzarini93c
Y 188 H/L	TAT→CAT/CTT	HIV-1 Specific RT Inhibitor (NNRTI)	α-APA (loviride)	Selected	?	Y		Staszewski96
Y 188 L	TAT→TTA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	Y	?	1000-fold increase in IC90	Young95
Y 188 L	TAT→?	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected		Y		Bacheler00
Y 188 L	TAT→TTA	HIV-1 Specific RT Inhibitor (NNRTI)	TIBO R82913	Selected	N	Y		Vandamme94

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 189 I	GTA→ATA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?	2-fold resistant	Kleim96
G 190 A	GGA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Selected	N	Y		Richman94
G 190 A	GGA→GCA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	N	Y		Bacheler00
G 190 C	GGA→?	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 C	GGA→?	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 E	GGA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	AAP-BHAP (U-104489)	Selected	Y	?	T139I/G190E/T200A/L214F: >100. Additional mutations possibly restore the replication capacity of the G190E mutant	Olmsted96
G 190 E	GGA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 E	GGA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	N	Y		Bacheler00
G 190 E	GGA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?	Reduces enzymatic activity of RT and viral replication competency	Kleim95
G 190 E	GGA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	S-2720 (quinoxaline)	Selected	Y	?		Kleim93
G 190 E	GGA→GAA	HIV-1 Specific RT Inhibitor (NNRTI)	UC-38	Selected	Y	N	Selected In combination with G190E: > 100-fold	Balzarini95
G 190 Q	GGA→CAA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 Q	GGA→CAA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 Q	GGA→CAA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?	Appears exclusively in connection with V179D	Kleim96
G 190 R	GGA→AGA	noncompetitive RT inhibitor	MSK-076	Selected	Y	?		Auwerx04
G 190 S	GGA→TCA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
G 190 S	GGA→TCA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	N	Y		Bacheler00
G 190 T	GGA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 T	GGA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 T	GGA→ACA	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Selected	Y	?	Appears during selection with low drug concentrations.	Kleim97
G 190 V	GGA→GTA	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 190 V	GGA→GTA	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	Y	Y	Mutation from patient database of isolates >10-fold resistant to NVP and EFV, but hypersuscpetible to DLV.	Huang03
G 196 E	GGG→GAG	NNRTI	BI-RG-587 (nevirapine) or DMP-266 (efavirenz)	Selected	?	Y	mutation selected in conjunction with K103N in one patient and V108I and Y181C in another	Ochoa de Echaguen05
E 203 K		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
H 208 Y		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
H 208 Y	CAT→TAT	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine)	Cross-R	?	Y	Polymorphism facilitating AZT+3TC dual resistance	Kemp98
H 208 Y	CAT→TAT	Pyrophosphate Analogue RT Inhibitor	PFA (foscarnet)	Selected	Y	Y	2-fold alone; Q161L/H208Y: 9-fold; suppresses effects of AZT mutations	Mellors95
L 210 W	TTG→TGG	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	Y	210W/215Y: 42-fold 41L/210W/215Y: 49-fold 41L/67N/70R/210W/215Y: 366-fold Mutation arises after prolonged AZT therapy.	Gurusinghe95, Harrigan96, Hooker96
R 211 K	AGG→AAG	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine)	Cross-R	?	Y	Polymorphism facilitating AZT+3TC dual resistance in association with M184V and other AZT resistance mutations.	Kemp98
L 214 F	CTT→TTT	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	?	Selection of resistant HIV-1EVK passaged in MT-4 cells	Gashnikova03
L 214 F	CTT→TTT	Nucleoside RT Inhibitor (NRTI)	ph-AZT	Selected	Y	?	Selection of resistant HIV-1EVK passaged in MT-4 cells	Gashnikova03
T 215 F	ACC→TTC	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	?	Y	K67N/K70R/T215Y/K219Q: 120-fold	Larder89, Larder91, Kellam92

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
T 215 Y	ACC→TAC	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	Y	M41L/T215Y: 60–70-fold; K67N/K70R/T215Y/K219Q: 120-fold. Effect of T215Y is reversed by a ddI mutation (L74V), NNRTI mutations (L100I;Y181C) or (-)-FTC/3TC mutations (M184I/V)	Larder89, Larder91, Kellam92
D 218 E		Nucleoside RT Inhibitor (NRTI)		Selected		Y		Svicher06
K 219 E	AAA→GAA	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	Y	N		Larder89, Larder91, Kellam92
K 219 E	AAA→GAA	NRTI	PMPA (tenofovir)	Selected	?	Y		Wirden05
K 219 N	AAA→AAT	NRTI	PMPA (tenofovir)	Selected	?	Y		Wirden05
K 219 Q	AAA→CAA	Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	?	Y	K67N/K70R/T215Y/K219Q: 120-fold	Larder89, Larder91, Kellam92
K 219 R	AAA→AGA	Multiple Nucleoside	3TC (lamivudine) + d4T (stavudine)	Selected	?	Y	Seen in two patient on 3TC + d4T combination therapy.	Lawrence99
K 219 R	AAA→AGA	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine)	Selected	?	Y	Seen in two patient on AZT + 3TC combination therapy.	Lawrence99
K 219 W	AAA→TGG	Multiple Nucleoside	ddC (zalcitabine) + d4T (stavudine)	Selected	?	Y	Seen in one patient on ddC + d4T combination therapy.	Lawrence99
P 225 H	CCT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Selected	N	Y	Observed frequently in patients.	Bacheler00
P 225 H	CCT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	HBY 097	Cross-R	Y	?	S-2720-selected double mutant V106A/P225H: 4.0-fold	Pelemans97
P 225 H	CCT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	I-EBU (emivirine)	Cross-R	Y	?	S-2720-selected double mutant V106A/P225H: 5.7-fold	Pelemans97
P 225 H	CCT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	S-2720 (quinoxaline)	Selected	Y	?	P225H follows V106A. Also seen with L101I and Y181C.	Pelemans97
P 225 H	CCT→CAT	HIV-1 Specific RT Inhibitor (NNRTI)	UC-781	Cross-R	Y	?	S-2720-selected double mutant V106A/P225H: 3.7-fold	Pelemans97
F 227 C	TTC→TGC	HIV-1 Specific RT Inhibitor (NNRTI)	TMC125	Cross-R	Y	Y		Vingerhoets04
F 227 L	TTA→CTC	HIV-1 Specific RT Inhibitor (NNRTI)	S-1153	Selected	Y	?	V106A + F227L: 387-fold. This mutation confers hypersensitivity to delavirdine.	Fujiwara98
F 227 L		NNRTI	VRX-480776	Selected	Y			Zhang06b
V 233 E	GAA→GTA	Multiple Nucleoside	AZT (zidovudine) + BHAP U-87201E (atevirdine)	Selected	N	Y	Seen in 1 patient. K101E, Y188H and K238T also seen in patients on ATV/AZT combination therapy.	Demeter98
L 234 I	CTC→ATC	HIV-1 Specific RT Inhibitor (NNRTI)	S-1153	Selected	Y	?	This mutation confers hypersensitivity to loviride.	Fujiwara98
P 236 L	CCT→CTT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-87201E (atevirdine)	Selected	Y	?	Sensitizes RT 10-fold to nevirapine, TIBO R82913 and L-697,661	Dueweke93

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
P 236 L	CCT→CTT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Selected	Y	?	Sensitizes RT 10-fold to nevirapine, TIBO R82913 and L-697,661	Dueweke93
P 236 L	CCT→CTT	HIV-1 Specific RT Inhibitor (NNRTI)	HEPT	Selected	Y	?		Buckheit95c
K 238 S	AAA→AGT	NNRTI	BI-RG-587 (nevirapine)	Cross-R	Y	Y		Hachiya04
K 238 T	AAA→ACA	Multiple Nucleoside	AZT (zidovudine) + BHAP U-87201E (atevirdine)	Selected	N	Y	Seen in 1 patient. K101E, K103N, Y188H, and V233E also observed with ATV/AZT combination therapy.	Demeter98
K 238 T	AAA→ACA	Multiple Nucleoside	AZT (zidovudine) + BHAP U-87201E (atevirdine)	Selected	N	Y	Seen in 1 patient. K101E, K103N, Y188H and E233V also seen in patients on ATV/AZT combination therapy.	Demeter98
L 283 I	CTT→ACT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. Confers resistance in conjunction with mutations at codon 135.	Brown00
L 283 I	CTT→ACT	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. Confers resistance in conjunction with mutations at codon 135.	Brown00
L 283 I	CTT→ACT	HIV-1 Specific RT Inhibitor (NNRTI)	DMP-266 (efavirenz)	Cross-R	N	Y	Identified by logistic regression analysis, confirmed by mutagenesis studies. Confers resistance in conjunction with mutations at codon 135.	Brown00
E 312 Q		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
Y 318 F	TAT→TTT	HIV-1 Specific RT Inhibitor (NNRTI)	BHAP U-90152 (delavirdine)	Cross-R	Y	Y	This mutation also acts synergistically with K103N and Y181C to confer higher levels of resistance to DLV and EFV than seen with either of these mutations alone	Harrigan02, Pelemans98
Y 318 F	TAT→TTT	HIV-1 Specific RT Inhibitor (NNRTI)	BI-RG-587 (nevirapine)	Cross-R	Y	Y	This mutation also acts synergistically with K103N and Y181C to confer higher levels of resistance to DLV and EFV than seen with either of these mutations alone	Harrigan02, Pelemans98
G 333 D	GGC→GAC	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine)	Cross-R	Y	Y	Facilitates dual resistance to AZT+3TC in association with M184V and standard AZT resistance mutations.	Kemp98

HIV-1 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
G 333 D	GGC→GAC	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine) + 1592U89 (abacavir)	Cross-R	?	Y	found in non-B subtypes	Caride00
G 333 E	GGC→GAG	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine)	Cross-R	Y	Y	Facilitates dual resistance to AZT+3TC in association with M184V and standard AZT resistance mutations.	Kemp98
G 333 E	GGC→GAG	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine) + 1592U89 (abacavir)	Cross-R	?	Y	found in non-B subtypes	Caride00
G 335 C		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
G 335 D		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
N 348 I		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
A 360 I		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
A 360 V		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
V 365 I		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
T 369 I		NNRTI	VRX-480775	Selected	Y			Zhang06b
A 376 S		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected		Y		Nikolenka06
T 386 I	ACT→ATT	Multiple Nucleoside	AZT (zidovudine) + 3TC (lamivudine) + 1592U89 (abacavir)	Cross-R	?	Y	Abrogates M184V suppression of L210W and L210W/G333D/E	Caride00

HIV-2 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 5 V		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
I 5 V	ATT→GTT	NRTI	multi-nucleoside	Selected	?	Y		Colson05
I 10 V		Nucleoside RT Inhibitor (NRTI)	1592U89(abacavir)+3TC (lamivudine)+AZT (zidovudine)	Selected	?	Y		Brandin03
I 10 V		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
V 11 I		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
R 20 K		Nucleoside RT Inhibitor (NRTI)	1592U89(abacavir)+3TC (lamivudine)+AZT (zidovudine)	Selected	?	Y		Brandin03
K 35 R	AAA→AGA	NRTI	multi-nucleoside	Selected	?	Y		Colson05
R 35 K		Nucleoside RT Inhibitor (NRTI)	1592U89(abacavir)+3TC (lamivudine)+AZT (zidovudine)	Selected	?	Y		Brandin03
K 40 R		Nucleoside RT Inhibitor (NRTI)	1592U89(abacavir)+3TC (lamivudine)+AZT (zidovudine)	Selected	?	Y		Brandin03
I 43 I		Nucleoside RT Inhibitor (NRTI)	ABT-538(ritonavir) + AG-1343 (nelfinavir)	Selected	?	Y		Brandin03
K 45 R		Nucleoside RT Inhibitor (NRTI)	ABT-538(ritonavir) + AG-1343 (nelfinavir)	Selected	?	Y		Brandin03
G 48 A		Nucleoside RT Inhibitor (NRTI)	ABT-378 (lopinavir)	Selected	?	Y		Brandin03
I 50 V		Nucleoside RT Inhibitor (NRTI)	ABT-378 (lopinavir)	Selected	?	Y		Brandin03
I 54 M		Nucleoside RT Inhibitor (NRTI)	ABT-538(ritonavir) + AG-1343 (nelfinavir)	Selected	?	Y		Brandin03

HIV-2 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 64 V		Nucleoside RT Inhibitor (NRTI)	ABT-378 (lopinavir)	Selected	?	Y		Brandin03
K 65 R		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
N 69 S		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
K 70 S		Nucleoside RT Inhibitor (NRTI)	1592U89(abacavir)+3TC (lamivudine)+AZT (zidovudine)	Selected	?	Y		Brandin03
V 71 I		Nucleoside RT Inhibitor (NRTI)	ABT-538(ritonavir) + AG-1343 (nelfinavir)	Selected	?	Y		Brandin03
A 92 T		Nucleoside RT Inhibitor (NRTI)	ABT-538(ritonavir) + AG-1343 (nelfinavir)	Selected	?	Y		Brandin03
L 99 F		Nucleoside RT Inhibitor (NRTI)	ABT-538(ritonavir) + AG-1343 (nelfinavir)	Selected	?	Y		Brandin03
A 101 P	GCC→CCC	noncompetitive RT inhibitor	MSK-076	Selected	Y	?	Mutation found in HIV-2 at a position equivalent to the NNRTI binding site in HIV-1	Auwerx04
G 112 E	GGG→GAG	noncompetitive RT inhibitor	MSK-076	Selected	Y	?	Mutation found close to the HIV-2 active site	Auwerx04
Q 151 M		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
Y 162 H		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
T 163 A		Nucleoside RT Inhibitor (NRTI)	1592U89(abacavir)+3TC (lamivudine)+AZT (zidovudine)	Selected	?	Y		Brandin03
M 184 V		Nucleoside RT Inhibitor (NRTI)	3TC (lamivudine)	Selected	?	Y		Brandin03

HIV-2 RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
F 214 L		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine) + 3TC (lamivudine) + ddI (didanosine)	Selected	?	Y		Brandin03
F 214 L	TTT→CTT	NRTI	multi-nucleoside	Selected	?	Y		Colson05
E 219 D		Nucleoside RT Inhibitor (NRTI)	AZT (zidovudine)	Selected	?	Y		Brandin03
K 223 R	AAA→AGA	NRTI	multi-nucleoside	Selected	?	Y		Colson05

SIV RT

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 65 R	AAA→AGA	SIV Nucleoside RT Inhibitor	PMPA (tenofovir)	Selected	?	Y	K65R appears first, followed by N69S and I118V. Observed changes at N69S and I118V do not result in increased resistance.	VanRompay96, Cherrington96a, VanRompay97a
Q 151 M	CAG→ATG	SIV Nucleoside RT Inhibitor	AZT (zidovudine)	Selected	?	Y		VanRompay97

HIV-1 Integrase

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
T 66 I		Integrase Inhibitor	Dihydroxythiophene (DHT)	Cross R	Y		Double mutants T66I/N155S confer 17–25 fold resistance while triple mutants T66I/S153Y/N155S confers greater than 33 fold resistance. DHTs are a novel series of inhibitors; two are described in this paper DHT-1 and DHT-2.	Kehlenbeck06
G 140 S	GGC→AGC	Integrase inhibitor	L-Chicoric Acid	Selected	Y	?	Mutation located in the catalytic core of integrase. Mildly attentuates virus growth.	King98
S 153 Y		Integrase Inhibitor	Dihydroxythiophene	Cross R	Y		Double mutants T66I/N155S confer 17–25 fold resistance while triple mutants T66I/S153Y/N155S confers greater than 33 fold resistance. DHTs are a novel series of inhibitors; two are described in this paper DHT-1 and DHT-2.	Kehlenbeck06
N 155 S		Integrase Inhibitor	Dihydroxythiophene	Cross R	Y		Double mutants T66I/N155S confer 17–25 fold resistance while triple mutants T66I/S153Y/N155S confers greater than 33 fold resistance. DHTs are a novel series of inhibitors; two are described in this paper DHT-1 and DHT-2.	Kehlenbeck06
V 165 I		Integrase inhibitor	FZ41	Selected	?	Y	selected in conjunction with V249I; double mutant confers 9 fold resistance	Bonnenfant04
F 185 K		integrase inhibitor	DKA (β-diketo acids)	Cross-R	Y	?	only biochemical studies done to test decrease in susceptibility	Marchand03
V 249 I		Integrase inhibitor	FZ41	Selected	?	Y	selected in conjunction with V165I; double mutant confers 9 fold resistance	Bonnenfant04
C 280 S		integrase inhibitor	DKA (β-diketo acids)	Cross-R	Y	?	only biochemical studies done to test decrease in susceptibility	Marchand03
C 280 Y		Integrase inhibitor	FZ41	Selected	?	Y	confers 5 fold resistance	Bonnenfant04

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Q 32 H		Fusion/Binding Inhibitor	T20 (pentafuside)	Selected		Y	found in combination with G36D in patients	Wei02
Q 32 R		Fusion/Binding Inhibitor	T20 (pentafuside)	Selected		Y	found in combination with G36D in patients	Wei02
L 33 S	TTA→TCA	fusion inhibitor	M87	Selected	Y	?	Enhances viral fitness	Lohrengel05
G 36 D	GGT→GAT	Fusion/Binding Inhibitor	T20 (pentafuside)	Selected	Y	Y	Resistance lost when R122G substitution is present in HR2 domain	Wei02
G 36 S	GGT→AGT	Fusion/Binding Inhibitor	T20 (pentafuside)	Selected	Y	?	Both G36S and V38M mutations must be present to confer resistance.	Rimsky98
G 36 V	GGT→GTT	fusion inhibitor	T20 (enfuvirtide)	Selected	?	Y		Menzo04
I 37 V		Fusion/Binding Inhibitor	T20 (pentafuside)	Selected		Y		Wei02
V 38 A	GTG→GCG	Fusion/Binding Inhibitor	T20 (pentafuside)	Selected	Y	Y		Wei02
V 38 M	GTG→ATG	Fusion/Binding Inhibitor	T20 (pentafuside)	Selected	Y	?	Both G36S and V38M mutations must be present to confer resistance.	Rimsky98
Q 39 R		Fusion/Binding Inhibitor	T20 (pentafuside)	Selected		Y	found in combination with G36D in patients	Wei02
N 42 D	AAC→GAC	fusion inhibitor	T20 (enfuvirtide)	Selected	?	Y		Menzo04
N 42 T	AAC→ACC	fusion inhibitor	T20 (enfuvirtide)	Selected	?	Y		Menzo04
N 43 D	AAT→GAC	fusion inhibitor	T20 (enfuvirtide)	Selected	?	Y		Menzo04
L 44 M	TTG→ATG	fusion inhibitor	T20 (enfuvirtide)	Selected	?	Y		Menzo04
L 45 M	TTG→ATG	fusion inhibitor	T20 (enfuvirtide)	Selected	?	Y		Menzo04
R 46 M	AGG→ATG	Fusion/Binding Inhibitor	T20 (pentafuside)	Selected		Y		Wei02
I 48 V	ATT→GTT	fusion inhibitor	M87	Selected	Y	?	Double mutant I48V/N126K results in strong reduction of viral fitness	Lohrengel05
V 68 A		Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in gp120.	Lin03
V 69 I	GTC→ATC	Fusion/Binding Inhibitor	T20 (pentafuside)	Selected		Y	represents a conservative change that is present in the HIV-1 LAI consensus sequence	Wei02
I 84 S	ATC→AGC	Fusion/Binding Inhibitor	RPR103611	Selected	Y	?		Labrosse97
N 106 K	AAT→AAG	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
N 106 K	AAT→AAG	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
N 106 K	AAT→AAG	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
N 106 K	AAT→AAG	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
S 113 N	AGT→AAT	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	ND	V1 Loop Region	Este96a, Este97

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
N 126 K	AAT→AAA	fusion inhibitor	M87	Selected	Y	?	Double mutant I48V/N126K results in strong reduction of viral fitness	Lohrengel05
S 134 N	AGC→AAC	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	?	V2 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	Este97, Este96a
S 134 N	AGC→AAC	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
S 134 N	AGC→AAC	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
S 134 N	AGC→AAC	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
S 134 N	AGC→AAC	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
F 145 L	TTC→TTA	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
F 145 L	TTC→TTA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?	Combination of mutations: 2- to 100-fold	DeVreese96, DeVreese96a
F 145 L	TTC→TTA	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
F 145 L	TTC→TTA	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
F 145 L	TTC→TTA	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
N 188 K	AAT→AAA	Fusion/Binding Inhibitor	siamycin I	Selected	Y	?	N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	Lin96
P 203 L		Entry Inhibitor	Amphotericin B Methyl Ester (AME)	Selected	Y		Mutations selected in the cytoplasmic tail of gp41	Waheed06
N 204 K		entry inhibitor	Concanavalin A (ConA)	Selected	Y	?	mutations in gp120	Witvrouw05
S 205 L		Entry Inhibitor	Amphotericin B Methyl Ester (AME)	Selected	Y		Mutations selected in the cytoplasmic tail of gp42	Waheed06
G 237 R		Fusion/Binding Inhibitor	IC9564 (emivirine)	Selected	Y	?	gp-120	Holz-Smith01
F 245 I	TTC→ATC	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
F 245 I	TTC→ATC	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
F 245 I	TTC→ATC	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
F 245 I	TTC→ATC	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
R 252 K		Fusion/Binding Inhibitor	IC9564 (emivirine)	Selected	Y	?	gp-120	Holz-Smith01
S 261 F		entry inhibitor	Concanavalin A (ConA)	Selected	Y	?	mutations in gp120	Witvrouw05
K 269 E	AAA→GAA	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	?	V3 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	Este97, Este96a
N 269 E	AAC→GAA	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
N 269 E	AAC→GAA	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
N 269 E	AAC→GAA	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
N 269 E	AAC→GAA	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
N 269 K	AAC→?	Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
N 269 K	AAC→?	Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
N 269 K	AAC→?	Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
N 269 K	AAC→?	Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
N 269 K	AAC→?	Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
N 269 K	AAC→?	Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
N 270 S	AAT→AGT	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
R 272 T	AGA→ACA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
S 274 del		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
S 274 del		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
S 274 del		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
S 274 del		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
S 274 del		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
S 274 del		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
S 274 R	AGT→AGA	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?	Combination of mutations: 95- to 792-fold	DeVreese96, DeVreese96a
S 274 R	AGT→AGA	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?		DeVreese96, DeVreese96a
S 274 R	AGT→AGA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
I 275 del		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 275 del		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
I 275 del		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
I 275 del		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
I 275 del		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
I 275 del		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
Q 278 H	CAG→CAT	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	?	V3 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	Este97, Este96a
Q 278 H	CAG→CAT	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
Q 278 H	CAG→CAT	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?		DeVreese96, DeVreese96a
Q 278 H	CAG→CAC	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?		DeVreese96, DeVreese96a

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Q 278 H	CAG→CAC	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
Q 278 H	CAG→CAT	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
Q 278 H	CAG→CAT	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
Q 278 H	CAG→CAT	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
Q 278 T	CAG→ACG	Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
Q 278 T	CAG→ACG	Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
Q 278 T	CAG→ACG	Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
Q 278 T	CAG→ACG	Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Q 278 T	CAG→ACG	Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
Q 278 T	CAG→ACG	Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
R 279 K		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
R 279 K		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
R 279 K		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
R 279 K		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
R 279 K		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
R 279 K		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
A 284 V		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
A 284 V		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
A 284 V		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
A 284 V		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
A 284 V		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
A 284 V		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
F 285 L		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
F 285 L		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
F 285 L		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
F 285 L		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
F 285 L		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
F 285 L		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
V 286 Y		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
V 286 Y		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
V 286 Y		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
V 286 Y		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
V 286 Y		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
V 286 Y		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
I 288 T	ATA→ACA	Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
I 288 T	ATA→ACA	Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
I 288 T	ATA→ACA	Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
I 288 T	ATA→ACA	Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
I 288 T	ATA→ACA	Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
I 288 T	ATA→ACA	Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
I 288 V	ATA→GTC	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
I 288 V	ATA→GTA	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?	Combination of mutations	DeVreese96a
I 288 V	ATA→GTA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
I 288 V	ATA→GTC	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
I 288 V	ATA→GTC	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
I 288 V	ATA→GTC	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
ins 290 T		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
ins 290 T		Fusion/Binding Inhibitor	AMD3100	Selected	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
ins 290 T		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
ins 290 T		Fusion/Binding Inhibitor	T134	Cross Resistant	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
ins 290 T		Fusion/Binding Inhibitor	T140	Selected	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
ins 290 T		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
K 290 E		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
K 290 E		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
K 290 E		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
K 290 E		Fusion/Binding Inhibitor	T134	Cross Resistant	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
K 290 E		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
K 290 E		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	?	V3 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	Este97, Este96a
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
N 293 D	AAT→GAT	Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01
N 293 H	AAT→CAT	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
M 294 I	ATG→ATC	Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
M 294 I	ATG→ATC	Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
M 294 I	ATG→ATC	Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
M 294 I	ATG→ATC	Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
M 294 I	ATG→ATC	Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
M 294 I	ATG→ATC	Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
Q 296 K		Fusion/Binding Inhibitor	ALX40–4C	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 145-fold cross-resistant to ALX40–4C. Role of each mutation not confirmed by site-directed m	Kanbara01
Q 296 K		Fusion/Binding Inhibitor	AMD3100	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 15-fold cross-resistant to AMD3100. Role of each mutation not confirmed by site-directed mut	Kanbara01
Q 296 K		Fusion/Binding Inhibitor	SDF-1	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 26-fold cross-resistant to SDF-1. Role of each mutation not confirmed by site-directed mutag	Kanbara01
Q 296 K		Fusion/Binding Inhibitor	T134	Selected	Y	N	In vitro selected virus (p145 of HIV-1NL4–3, contains mutations N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275 in V3 loop of gp120) 15-fold resistant to T134. Role of each mutation not conf	Kanbara01
Q 296 K		Fusion/Binding Inhibitor	T140	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 21-fold cross-resistant to T140. Role of each mutation not confirmed by site-directed mutag	Kanbara01
Q 296 K		Fusion/Binding Inhibitor	vMIP-II	Cross Resistant	Y	N	T134-resistant virus (selected in vitro, contains N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; 290Tins, D274–275) 42-fold cross-resistant to vMIP II. Role of each mutation not confirmed by site-directed mut	Kanbara01

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
A 297 T	GCA→ACA	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?		DeVreese96, DeVreese96a
N 302 K	AAA	entry inhibitor	Concanavalin A (ConA)	Selected	Y	?	mutations in gp120	Witvrouw05
N 302 K	AAA	entry inhibitor	Cyanovirin (CV-N)	Selected	Y	?	mutations in gp120	Witvrouw05
H 308 P		Fusion/Binding Inhibitor	AD101	Selected	Y	?	Small molecule entry inhibitor. Mutation in gp120V3. Primary R5 isolate, CC1/85 passaged in PMBC in increasing concentrations of CCR5-inhibitor AD101. When tested in combination with K305R, H308P, A316V and G321E, fold-R was $>5 \times 10^6$	Kuhmann04, Trkola02
T 311 I		entry inhibitor	Concanavalin A (ConA)	Selected	Y	?	mutations in gp120	Witvrouw05
N 323 S	AAT→AGT	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	?	C3 region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	Este97, Este96a
G 332 E	GGA→GAA	Fusion/Binding Inhibitor	siamycin I	Selected	Y	?	N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	Lin96
I 339 T	ATT→ACT	Fusion/Binding Inhibitor	NeoR6	Selected	Y	?	Mutation in gp120. Found in combination with S372L, Q395K, S668R, F672Y.	Borkow03
I 339 T	ATT→ACT	Fusion/Binding Inhibitor	R3G	Cross-R	Y	?	Mutation in gp120. Tested against NeoR6-resistant virus passaged in vitro. Virus contains mutations I339T, S372L, Q395K, S668R and F672Y.	Borkow03
N 351 D	AAT→GAT	Fusion/Binding Inhibitor	siamycin I	Selected	Y	?	N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	Lin96
S 372 L	TCA→TTA	Fusion/Binding Inhibitor	NeoR6	Selected	Y	?	Mutation in gp120. Found in combination with I339T, Q395K, S668R, F672Y.	Borkow03
S 372 L	TCA→TTA	Fusion/Binding Inhibitor	R3G	Cross-R	Y	?	Mutation in gp120. Tested against NeoR6-resistant virus passaged in vitro. Virus contains mutations I339T, S372L, Q395K, S668R and F672Y.	Borkow03
S 375 W		Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in CD4 contact site.	Lin03
R 378 T	AGA→ACA	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
R 378 T	AGA→ACA	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
R 378 T	AGA→ACA	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
R 378 T	AGA→ACA	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
P 385 L	CCA→CTA	Fusion/Binding Inhibitor	JM-2763	Selected	Y	?		DeVreese96, DeVreese96a
P 385 L	CCA→CTA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
R 387 I	AGA→ACA	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y	?	CD4 binding region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	Este97, Este96a
Q 395 K	CAG→AAG	Fusion/Binding Inhibitor	NeoR6	Selected	Y	?	Mutation in gp120 Found in combination with I339T, S372L, S668R, F672Y.	Borkow03
Q 395 K	CAG→AAG	Fusion/Binding Inhibitor	R3G	Cross-R	Y	?	Mutation in gp120. Tested against NeoR6-resistant virus passaged in vitro. Virus contains mutations I339T, S372L, Q395K, S668R and F672Y.	Borkow03
Q 410 E	CAA→GAA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
N 418 S		entry inhibitor	Cyanovirin (CV-N)	Selected	Y	?	mutations in gp120	Witvrouw05
M 426 L	ATG→TTG	Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in gp120.	Lin04, Lin03
W 427 V		Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in CD4 contact site.	Lin03
S 433 P	TCC→CCC	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
M 434 I	ATG→?	Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in gp120.	Lin04, Lin03
S 440 R		Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in gp120.	Lin03
V 457 I	GTA→ATA	Fusion/Binding Inhibitor	JM-3100	Selected	Y	?		DeVreese96, DeVreese96a
M 475 I	ATG→?	Fusion/Binding Inhibitor	BMS-488043	Selected	Y	?	Mutation in gp120.	Lin04, Lin03
A 550 T	GCC→ACC	Fusion/Binding Inhibitor	siamycin I	Selected	Y	?	N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	Lin96
Q 574 R		Entry Inhibitor	Retrocyclin-101 (RC-101)	Selected	Y		Substitution in gp160 at position 574, corresponding to the HR1 domain of gp41	Cole06
N 633 D	AAT→GAT	Fusion/Binding Inhibitor	siamycin I	Selected	Y	?	N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	Lin96
S 668 R	AGT→AGA	Fusion/Binding Inhibitor	NeoR6	Selected	Y	?	Mutation in gp41. Found in combination with I339T, S372L, Q395K, F672Y.	Borkow03
S 668 R	AGT→AGA	Fusion/Binding Inhibitor	R3G	Cross-R	Y	?	Mutation in gp41. Tested against NeoR6-resistant virus passaged in vitro. Virus contains mutations I339T, S372L, Q395K, S668R and F672Y.	Borkow03

HIV-1 Env

Amino Acid Change	Codon Change	Drug Class	Compound	Selected or Cross-R	In vitro	In vivo	Comments	Refs
F 672 Y	TTT→TAT	Fusion/Binding Inhibitor	NeoR6	Selected	Y	?	Mutation in gp41. Found in combination with I339T, S372L, Q395K, S668R.	Borkow03
F 672 Y	TTT→TAT	Fusion/Binding Inhibitor	R3G	Cross-R	Y	?	Mutation in gp41. Tested against NeoR6-resistant virus passaged in vitro. Virus contains mutations I339T, S372L, Q395K, S668R and F672Y.	Borkow03
L 762 S	TTG→TCG	Fusion/Binding Inhibitor	siamycin I	Selected	Y	?	N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	Lin96
FNSTW 364–368 Deletion	TTT AAT AGT ACT TGG	Fusion/Binding Inhibitor	DS (dextran sulphate)	Selected	Y			Este97
FNSTW 364–368 Deletion	Deletion	Fusion/Binding Inhibitor	JM 2763	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10 fold	Schols98
FNSTW 364–368 Deletion	Deletion	Fusion/Binding Inhibitor	JM-3100	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 10-fold	Schols98
FNSTW 364–368 Deletion	Deletion	Fusion/Binding Inhibitor	Mab 12G5	Cross Resistant	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T:	Schols98
FNSTW 364–368 Deletion	Deletion	Fusion/Binding Inhibitor	SDF-1α	Selected	Y	?	106K/134N/145L/245I/269E/278H/288V/293D/364–367Deletion/387T: 15-fold.	Schols98
deletion 364–376		entry inhibitor	Cyanovirin (CV-N)	Selected	Y	?	mutations in gp120	Witvrouw05

Abbreviations used in tables

Amino acids

A	alanine
C	cysteine
D	aspartate
E	glutamate
F	phenyalanine
G	glycine
H	histidine
I	isoleucine
K	lysine
L	leucine
M	methionine
N	asparagine
P	proline
Q	glutamine
R	arginine
S	serine
T	threonine
V	valine
W	tryptophan
Y	tyrosine

Drug class

F/BI	Fusion/Binding Inhibitor
II	Integrase Inhibitor
MN	Multiple Nucleoside
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	HIV-1 Specific Nonnucleoside RT Inhibitor
PI	Protease Inhibitor
PARTI	Pyrophosphate Analogue RTI
SIV RTI	SIV Nucleoside RTI

Compounds

Compound	Other Names (Company)	Chemical Name or Description
(-)-dOTC	BCH-10652	(-)-2′-deoxy-3′-oxa-4′-thiocytidine
(-)-dOTFC		(-)-2′-deoxy-3′-oxa-4′-thio-5-fluorocytidine
(-)-FTC	Emtricitabine, Coviracil (Triangle Pharmaceuticals)	(-)-(2*R*,5*S*)-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
(+)-dOTC		(+)-2′-deoxy-3′-oxa-4′-thiocytidine
(+)-dOTFC		(+)-2′-deoxy-3′-oxa-4′-thio-5-fluorocytidine
1737		Tetrahydronapthalene lignan derivative
1592U89	Abacavir, Ziagen, ABC (Glaxo Wellcome)	(1*S*,4*R*)-4-[2-amino-6-cyclopropyl-amino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate
3TC	(-)-BCH-189, Lamivudine, Epivir (Glaxo Wellcome)	(-)-β-L-2′,3′-dideoxy-3′-thiacytidine
4′-Ed4T		2′,3′-Didehydro-3′-deoxy-4′-ethynylthymidine
8-chloro-TIBO	RO91767, R86183, tivirapine	(+)-(*S*)-4,5,6,7-Tetrahydro-8-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazol[4,5,1-jk][1,4]benzodiazepine
A-77003	C2 symmetry-based protease inhibitor (Abbott)	2PyridCH2NCH3CO-Val-NHCH(Bz)]CHOHCHOH
AAP-BHAP	U-104489 (Pharmacia & Upjohn)	1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[N-ethyl-N-[3-(1,1-dimethyl)amino]-2-pyridinyl]amino]piperidine
ABT-378	Aluviran, Lopinavir (Abbott)	N-[(1S,3S,4S)-4-[[2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide
ABT-538	Ritonovir, Norvir (Abbott)	10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester

Abbreviations (cont)

Compounds (cont)

AD101		
ADAMII		Methyl 3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate
AG1343	Nelfinavir, Viracept (Agouron)	(3*S*,4a*S*,8a*S*)-N-tert-Butyl-2-[(2*R*,3*R*)-3-(3,2-cresotamido)-2-hydroxy-4-(phenylthio)butyl]decahydro-3-isoquinoline-carboxamide monomethanesulfonate
ALX40-4C		a polypeptide of nine d-Arg residues
AMD3100		octahydrochloride dihydrate of 1,19-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane
Amphotericin B Methyl Ester		[2-[[(4E,6E,8E,10E,12E,14E,16E)-38-carboxy-19,25,27,30,31,33,35,37-octahydroxy-18,20,21-trimethyl-23-oxo-22,39-dioxabicyclo[33.3.1]nonatriaconta-4,6,8,10,12,14,16-heptaen-3-yl]oxy]-3,5-dihydroxy-6-methyl-oxan-4-yl]azanium chloride
AZT	zidovudine (Glaxo Wellcome)	3′-azido-3′-deoxythymidine
BHAP U-87201E	Atevirdine (Pharmacia Upjohn)	1-[(5-Methyoxyindol-2-yl)carbonyl]-4-[3-(ethylamino)-2-pyridyl]piperazine
BHAP U-88204E		1-(Indolyl-2-carbonyl)-4-[3-[(1-methylethyl)amino]pyridyl-piperazine
BHAP U-90152	Delavirdine, Rescriptor (Pharmacia Upjohn)	1-(5-Methanesulphonamido)-1H-indol-2-yl-carbonyl)-4-[3-(isopropylamino)-2-pyridinyl]piperazine
BHAP U-90153		bisheteroarylpiperidinyl derivative
BHAP U-90154		bisheteroarylpiperidinyl derivative
BHAP U-90155		bisheteroarylpiperidinyl derivative
BILA 1906 BS	(Bio-Mega/Boehringer Ingelheim)	N-{1*S*-[[[3-[2*S*-(1,1-dimethylethyl)amino]carbonyl-4*R*-]3-pyridinylmethyl)thio]-1-piperidinyl]-2*R*-hydroxy-1*S*-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl}-2-quinolinecarboxamide
BILA 2011	Palinavir (Bio-Mega/Boehringer Ingelheim)	N-{1*S*-[[[3-[2*S*-(1,1-dimethylethyl)amino]carbonyl]-4*R*-[4-pyridinylmethyl)oxy]-1-piperidinyl]-2*R*-hydroxy-1*S*-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl}-2-quinolinecarboxamide
BILA 2185 BS	(Bio-Mega/Boehringer Ingelheim)	N-(1,1-dimethylethyl)-1-[2*S*-[[2-2,6-dimethyphenoxy)-1-oxoethyl]amino]-2*R*-hydroxy-4-phenylbutyl]4*R*-pyridinylthio)-2-piperidine-carboxamide
BI-RG-587	Nevaripine, Viramune (Boehringer Ingleheim)	11-Cyclopropyl-4-methyl-5,11-dihydro-6H-dipyrido[3,2-b:2′,3′-e]-[1,4]diazepin-6-one
BM+51.0836		thiazolo-isoindolinone derivative
BMS-186318	(Bristol-Myers Squibb)	[1*S*-[1*R**,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[4-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-dimethylethyl-ester
BMS-232632	Atazanavir	azapeptide protease inhibitor
BMS-488043		
Calanolide A	NSC675451	a dipyranocoumarin
Concanavalin A	ConA	plant lectin from *Canavalia ensiformis*
Cyanovirin	CV-N, NSC 682999 (Cellegy Pharmaceuticals)	Protein from cyanobacterium *Nostoc ellipsosporum*

Abbreviations (cont)

Compounds (cont)

cyclo-d4G		β-D-6-cyclopropylamino-2′,3′-Didehydro-2′3′-Dideoxyguanosine
d-d4FC	D4FC, DPC 187	2′3′-Didehydro-2′ 3′ dideoxy -5-fluorocytidine
d4C		Didehydro-2′ 3′ dideoxy cytidine
d4T	Stavudine, Zerit (Bristol-Myers Squibb)	2′,3′-didehydro-3′-deoxythymidine
ddC	Zalcitabine, Hivid (Roche)	2′,3′-dideoxycytidine
ddI	Didanosine, Videx (Bristol-Myers Squibb)	2′,3′-dideoxyinosine
Dihydroxythiophene		
DKA		beta-diketo acids
DMP-266	Efavirenz, Sustiva (Dupont Merck)	(-)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4,-dihydro-2H-3,1-benzoxazin-one
DMP-323	XM-323 (Dupont Merck)	[4*R*-(4-α,5-α,6-β,7-β)]-hexahydro-5,6-dihydroxy-1,3-bis[(4-hydroxymethyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one
DMP-450	(Avid Therapeutics)	[4*R*-(4-α,5-α,6-β,7-β)]-hexahydro-5,6-bis(hydroxy)-1,3-bis(3-amino)phenyl]methyl)-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-onebismesylate
(+)dOTFC	(+)-dOTFC	(+)-2′-Deoxy-3′-oxa-4′-thio-5′-fluorocytidine
DS		dextran sulfate
DXG	(-)-β-dioxolane-G	(-)-(2*R*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]guanine
E-BPTU	NSC 648400	1-benzyloxymethyl-5-ethyl-6-(2-pyridylthio)uracil
EBU-dM		5-ethyl-1-ethoxymethyl-6-(3,5-dimethylbenzyl)uracil
E-EBU		5-ethyl-1-ethoxymethyl-6-benzyluracil
E-EPSeU		1-(ethoxymethyl)-(6-phenylselenyl)-5-ethyluracil
E-EPU		1-(ethoxymethyl)-(6-phenyl-thio)-5-ethyluracil
F-ddA	Lodenosine	2′-fluoro-2′,3′-dideoxyadenosine
FZ41		styrylquinoline
GW420867X		S-3-ethyl-6-fluoro-4-isopropoxycarbonyl-3,4-dihydro-quinoxalin-2(1H)-one
HBY 097		(*S*)-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin-2(1H)-thione
HEPT		1-[(2-hydroxyethoxy)methyl]6-(phenylthio)thymine
IC9564	Betulinic acid derivative	4*S*-[8-(28 betuliniyl) aminooctanoylamino]-3*R*-hydroxy-6-methylheptanoic acid
I-EBU	MKC-442, emivirine, coactinon (Triangle Pharmaceuticals)	6-benzyl-1-ethoxymethyl-5-isopropyluracil/
JE-2147		an allophenylnorstatine-containing dipeptide protease inhibitor
JM-2763	(Johnson Matthey)	1,10-(1,3-propanediyl)-bis-1,4,8,11-tetraazacyclo-tetradecane
JM-3100	SID791 (Johnson Matthey)	1,10-[1,4-phenylenebis-(methylene)]bis-(1,4,8,11-tetraazacyclotetradecane)octahydrochloride dihydrate
KNI-272	Kynostatin 272	(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid-containing tripeptide
L-697,593		5-ethyl-6-methyl-3-(2-phthalimido-ethyl)pyridin-2(1H)-one
L-697,661		3-[(-4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino-5-ethyl-6-methylpyridin-2(1H)-one
L-Chicoric acid		[S-(*R**,*R**)]-2,3-Bis[[3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]oxy]butanedioic acid

Abbreviations (cont)

Compounds (cont)

L-FddC		(-)-β-L-5-fluoro-2′,3′-dideoxy-cytidine
LY-300046 HCl	Trovirdine (Lilly/Medivir/Abbott)	N-[2-(2-pyridylethyl)-N′-[2-(5-bromopyridyl)thiourea,hydrochloride
M87		membrane anchored gp41 derived peptide
MK-639	Indinavir, Crixivan, L735,524 (Merck)	[1(1*S*,2*R*),5(*S*)]-2,3,5-Trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-erythro-pentonamide sulfate
MP-134		C2 symmetry-based protease inhibitor
MP-167		
MSK-076	(Medivir AB)	phenylmethylthiazolythiourea (PETT) derivative
NeoR6	hexa-arginine neomycin B conjugate	
no name		O-(2-Phenoxy ethyl)benzoyl (phenyl) thiocarbamate 17c
P-1946		methyl N-[(1S)-1-[[(5S)-5-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-6-hydroxy-hexyl]carbamoyl]-2-(1H-indol-3-yl)ethyl]carbamate
P9941	(Dupont Merck)	[2-pyridylacetyl-IIePheAla-y(CHOH)]$_2$
PA-457	Bevirimat (Panacos)	3-O-(3′, 3′−dimethylsuccinyl)betulinic acid
PFA	Foscarnet (Astra)	phosphonoformate
ph-AZT	5′-phosphit 3′ azido-2′3′-dideoxythymidine	
PMEA	adefovir (Gilead Sciences)	9-(2 phosphonylmethoxyethyl)adenine
PMPA	tenofovir (Gilead Sciences)	(*R*)-9-(2-phosphonyl-methoxypropyl)adenine
PNU-140690	Tipranavir, U-140690 (Pharmacia & Upjohn)	(6*R*)-3-(1*R*)-1-[3-([Trifluoromethyl)(2-pyridyl)]sulfonylamino)-phenyl]propyl-4-hydroxy-6-(2-phenylethyl)-6-propyl-5,6-dihydro-2H-pyran-2-one
QM96521		1,1,3-trioxo-2H,4H-thieno[2,4-3][1,2,4]thiadiazine derivative (TTD)
QYL-609		
QYL-685		methylenecyclopropane nucleoside analog with a phenylphosphoralaninate moiety
R3G		tri arginine gentamicin C conjugate
Retrocyclin-101	18-aa peptide GICRCICGKGICRCICGR	
Ro 31-8959	Saquinavir, Invirase, Fortovase (Roche)	N(1)-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-,[3*S*-[2[1*R**(*R**),2*S**],3α,4aβ,8aβ]]-, monomethanesulfonate
RPI-312		1-[(3*S*)-3-(n-alpha-benzyloxycarbonyl)-l-asparginyl)-amino-2-hydroxy-4-phenyl-butyryl]-n-tert-butyl-l-proline amide (peptidyl protease inhibitor)
RPR103611		a triterpene betulinic acid derivative
RO033-4649	(Roche)	
S-1153		5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1Himidazol-2-yl methyl carbamate
S-2720		6-chloro-3,3-dimethyl-4-(isopropenyl-oxycarbonyl)-3,4-dihydroquinoxalin-2(1H)thione

Abbreviations (cont)

Compounds (cont)

SC-52151	Telinavir	N-tert-butyl-N′-isobutyl-N′-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[4-amino-1,4-dioxo-2(*S*)-(2-quinolinylcarboxamido)butyl-amino]butyl]urea
SC-55389A	(Searle)	hydroxyethyl-urea isostere protease inhibitor
SDF-1		Stromal cell-derived factor 1
SDF-1α		Stromal cell-derived factor 1α
Siamycin I		21-residue tricyclic peptide
SKF108842		protease inhibitor
T134		[Tyr5,12, Lys7]-polyphemusin II-derivative with amino acid sequence R-R-W-C-Y-R-K-DK-P-Y-R-Ci-C-R-COOH
T140		[Tyr5,12, Lys7]-polyphemusin II-derivative
T20	DP-178, Pentafuside (Trimeris)	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
TIBO R82150	(Janssen)	(+)-(5*S*)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione
TIBO R82913	(Janssen)	(+)-(5*S*)-4,5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)-imidazo-[4,5,1-jk]-[1,4]benzo-diazepin-2(1H)-thione
TMC114	UIC-94017, Darunavir, Prezista (Tibotec)	[(1S,5R,8S)-4,6-dioxabicyclo[3.3.0]oct-8-yl] N-[(2S,3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-3-hydroxy-1-phenyl-butan-2-yl]carbamate
TMC125		
TSAO		[2′,5′-bis-O-(tert-butyldimethylsilyl)-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2″-dioxide)]-β-D-pentofuranosyl derivative
UC-10	NSC 645129 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-16	(Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-32	NSC 645542 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-38	NSC 629243 (Uniroyal Chemical Co)	4-chloro-3-(isopropoxycarbonyl)phenylcarbamothioic acid, O-isopropyl ester
UC-42	(Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-57	NSC 647014 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-68	NSC 638532 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-69	NSC 646989 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-70	NSC 638534 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-80	NSC 639475 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-81	NSC 615727 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-82	(Uniroyal Chemical Co)	N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-thiophenecarbothioamide
UC-84	NSC 615985 (Uniroyal Chemical Co)	thiocarboxanilide derivative
UC-581	NSC 645727 (Uniroyal Chemical Co)	
UC-781	(Uniroyal Chemical Co)	N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarbothioamide

Abbreviations (cont)

Compounds (cont)

UCO40	NSC650065	
UIC-94003		
VB 11,328	(Vertex)	Carbamic acid, [3-[[(4-methoxyphenyl)sulfonyl](cyclopentylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, tetrahydro-3-furanyl ester
vMIP-II		viral macrophage inflammatory protein II
VRX-329747		
VX-478	141W94, Amprenavir, Agenerase	Carbamic acid, ((1*S*,2*R*)-3-(((4-aminophenyl)sulfonyl)(2-methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-, (3*S*)-tetrahydro-3-furanyl ester
α-APA	R18893, loviride analog	(+)-2,6-Dichloro-α-[(2-acetyl-5-methylphenyl)amino]benzamide

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