HIV RESISTANCE TO INTEGRASE INHIBITORS

RESISTANCE TO RALTEGRAVIR (MK-0518, Isentress)

Raltegravir was the first integrase inhibitor to progress into Phase III clinical trials and became the first one to be approved for clinical use. Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients. Its potency and tolerability have made it an important option for first-line therapy, the treatment of highly antiretroviral-experienced patients, and regimen simplification.


Biochemical analysis have demonstrated that HIV-1 group O integrase shows higher susceptibility to raltegravir than the prototypic HIV-1 group M subtype B integrase.

HIV-2 resistant variants involving the Y143C pathway have been found in patients who previously developed N155H (Xu et al. AIDS Res Hum Retroviruses 2009; 25: 843-847), but the effect of Y143C on raltegravir susceptibility is not significant (Smith et al. AIDS 2011; 25: 2235-2241), except when associated with other resistance-related mutations such as for example, E92Q (Ni et al. Retrovirology 2011; 8: 68). Interestingly, in vitro studies demonstrated that Y143C counteracts the effects of N155H on reduced drug susceptibility (Ni et al. Retrovirology 2011; 8: 68).

An HIV-2<sub>ROD</sub> variant carrying mutations Q91R/I175M has been selected in vitro in the presence of raltegravir (Perez Bercoff et al. Retrovirology 2010; 7: 98). This variant showed a 13-fold increase in the IC<sub>50</sub> for the inhibitor.

**INTEGRASE**

![INTEGRASE](image)

Figure 5.1. Amino acid sequence of the HIV-1 integrase (strain HXB2). GenBank accession number K03455. Underlined sequence corresponds to the core domain of the enzyme.
Figure 5.2. Structural location of amino acids involved in resistance to raltegravir, in the core domain of HIV-1 integrase. The location of Mg$^{2+}$ is indicated in magenta. Coordinates were taken from Protein Data Bank file 1BIU (Goldgur et al. Proc Natl Acad Sci USA 1998; 95: 9150-9154). Core domains are presented as a dimer, although integrase may also function as a tetramer. A detailed structural analysis of the contribution of resistance mutations and the role of conformational flexibility in binding to strand-transfer inhibitors has been recently published (Mouscadet et al. Drug Resist Updates 2010; 13: 139-150).

**RESISTANCE TO ELVITEGRAVIR (Stribild, GS-9137, JTK-303, 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid)**

Elvitegravir showed an EC$_{50}$ of 1.7 nM in cell-based assays, and was found to be well tolerated and efficacious in clinical trials (Klibanov. Curr Opin Invest Drugs 2009; 10: 190-200). However, it has to be co-formulated with a CYP3A inhibitor. In August 2012, elvitegravir was approved for clinical use by the U.S. Food and Drug Administration as a component of Stribild, a co-formulation also containing the reverse transcriptase inhibitors tenofovir and emtricitabine and the pharmacokinetic enhancer cobicistat (DeJesus et al. Lancet 2012; 379: 2429-2438; Sax et al. Lancet 2012; 379: 2439-2448).

Early studies involving 40 patients showed that there was no evidence of resistance after three weeks of therapy (DeJesus et al. J Acquir Immune Defic Syndr 2006; 43: 1-5) and was rare in patients treated for 144 weeks (Kulkarni et al. HIV Clin Trials 2014; 15: 218-230). HIV-1 variants containing T66I/Q95K/Q146P/S147G (with or without E138K) were selected in cell culture at high concentrations of the inhibitor, while H51Y/E92Q/S147G/E157Q was selected at low concentrations. T66I and E92Q were the key mutations for acquisition of elvitegravir resistance, and by themselves increased resistance around 35-fold (Shimura et al.
Cross-reactivity with other integrase inhibitors such as L-731,988, L-870,810 and S-1360 was also observed in those experiments.

E92Q, Q148K/H/R and/or N155H mutations have been detected in a significant number of patients showing virological failure to elvitegravir. In some patients, a secondary mutation (L68I or L68V) may also appear. These mutations are usually linked to E92Q. L68V confers low-level resistance to elvitegravir [Goodman et al. Antivir Ther 2008; 13 (suppl. 3): A15]. P145S, a mutation selected in one patient by raltegravir was found to confer resistance to elvitegravir [Kobayashi et al. Antiviral Res 2008; 80: 213-222; Gallien et al. Antivir Ther 2010; 15 (suppl. 2): A15].


Sustained antiviral response to elvitegravir has been reported for one treatment-naïve patient infected with HIV-2 (group B) (Zhang et al. AIDS 2014; 28: 2329-2331). The inhibitor has been found to be effective in vitro against primate and non-primate lentiviruses, showed intermediate efficiency on mouse mammary tumour virus and murine leukemia virus and was ineffective against the Rous sarcoma virus (Koh et al. J Virol 2011; 85: 3677-3682). Group O HIV-1 isolates were 10-fold less susceptible to elvitegravir inhibition than group M HIV-1 (Tebit et al. AIDS Res Hum Retroviruses 2016; 32: 676-688).

Dolutegravir is a strand transfer inhibitor of HIV-1 integrase, developed from prototypical diketo acid structures (Hazuda. Curr Opin HIV AIDS 2012; 7: 383-389; Bailly & Cotelle. Expert Opin Drug Discov 2015; 10: 1243-1253). It has an IC₅₀ value of 2.7 nM in enzymatic assays and is active against HIV strains infecting PBMCs (EC₅₀ of 0.5 nM). Improved pharmacodynamic properties of dolutegravir versus first-generation strand transfer inhibitors (i.e. higher dose-response curve slope) are largely responsible for its potent antiviral activity (Laskey & Siliciano. JCI Insight 2016; 1: e89810). HIV-2 group A and group B isolates showed similar susceptibility to dolutegravir than HIV-1 isolates (Smith et al. Retrovirology 2015; 12: 10). As observed with other diketo acid inhibitors of the viral integrase, S153F and S153Y were selected in HIV-1 passaged in vitro in the presence of the drug (Kobayashi et al. Antimicrob Agents Chemother 2011; 55: 813-821).
SPRING trials in treatment-naïve individuals showed that dolutegravir (taken at doses of 10, 25 and 50 mg twice a day) was an effective inhibitor of HIV replication, non inferior to efavirenz (van Lunzen et al. Lancet Infect Dis 2012; 12: 111-118; Walmsley et al. J Acquir Immune Defic Syndr 2015; 70: 515-519; reviewed in Kandel & Walmsley. Drug Des Devel Ther 2015; 9: 3547-3555). SPRING-2 phase III clinical trials also showed at week 96 that once-daily dolutegravir was non-inferior to twice-daily raltegravir in naïve patients (Raffi et al. Lancet Infect Dis 2013; 13: 927-935). More recently, the SAILING study has shown that once-daily dolutegravir, in combination with two other antiretroviral drugs is well tolerated and shows more efficacy than twice-daily raltegravir in treatment-experienced patients (Cahn et al. Lancet 2013; 382: 700-708). Dolutegravir was approved by the U.S. Food and Drug Administration in August 2013 (for a review, see Ballantyne & Perry. Drugs 2013; 73: 1627-1637). The drug is currently used in antiretroviral naïve patients in association with abacavir/lamivudine or emtricitabine/tenofovir.

Dolutegravir has shown efficacy in vitro on raltegravir- and elvitegravir-resistant clinical isolates of HIV-1 containing mutations Y143R, Q148K, N155H and G140S/Q148H (Kobayashi et al. Antimicrob Agents Chemother 2011; 55: 813-821), although it has been reported that increased dolutegravir resistance via the Q148 pathway and secondary substitutions may occur in vitro at low concentrations of the drug (Seki et al. Antimicrob Agents Chemother 2015; 59: 2596-2606). However, VIKING I and II clinical trials showed that the use of dolutegravir in patients failing raltegravir therapy was effective only on those bearing HIV-1 integrase mutations Y143C/R or N115H, while only a third of those having Q148H/K/R mutations had a virological response to treatment with dolutegravir (Eron et al. J Infect Dis 2013; 207: 740-749; reviewed in Malet et al. Curr Opin Virol 2012; 2: 580-587). In these trials, virological failure due to resistance to dolutegravir was attributed to the accumulation of multiple integrase inhibitor resistance-related mutations (e.g. L74I/M, T97A, E138A/K, Q148H, N155H). Results from the Phase III VIKING study showed that the response to dolutegravir was significantly reduced in patients infected with HIV-1 variants containing the integrase mutation Q148H/K/R, plus two or more amino acid substitutions of the group formed by L74I, E138A/K/T and G140A/C/S (Castagna et al. J Infect Dis 2014; 210: 354-362).

Development of R263K is compatible with the presence of single amino-acid substitutions such as E92Q or N155H (Anstett et al. J Virol 2015; 89: 4681-4684). However, the combination of R266K with T66I, G140S, Y143R or Q148R is incompatible with high-level viral replication and the development of high-level resistance to dolutegravir (Anstett et al. J Virol 2015; 89: 4681-4684; Liang et al. J Virol 2015; 89: 11269-11274).

The double-mutant E138K/Q148K showed high-level resistance to the drug in phenotypic assays (Figure 5.3). The Q148H/K/R mutations did not affect susceptibility to dolutegravir in HIV-1 subtype C and HIV-2 isolates (Kobayashi et al. Antimicrob Agents Chemother 2011; 55: 813-821; Garrido et al. Antiviral Res 2011; 90: 164-167; Malet et al. J Antimicrob Chemother 2011; 66: 1481-1483), although Q148K confers some resistance in the context of HIV-2_ROD (Smith et al. Retrovirology 2015; 12: 10). Clinical studies have shown that dolutegravir-containing regimens provide substantial initial efficacy in heavily-treated HIV-2-infected patients with virus lacking mutations at codons 148 and 155 in the integrase-coding region. These data suggest that cross-resistance of raltegravir and

Selection experiments carried out in cord blood monocytic cells using HIV-1 clones of subtypes B, C and A/G yielded the R263K mutation (Quashie et al. J Virol 2012; 86: 2696-2705). This mutation affecting a residue of the C-terminal domain of HIV-1 integrase conferred low-level resistance to the inhibitor. R263K was also identified in selection studies carried out with elvitegravir and confers low-level resistance to this inhibitor (Margot et al. Antiviral Res 2012; 93: 288-296). R263K has a relatively small effect on dolutegravir resistance when tested with the PhenoSense® Integrase assay (Monogram Biosciences) (i.e. barely 2-fold increase in the IC_{50} relative to the wild-type HIV-1_{NL4-3}) (Mesplède et al. Retrovirology 2013; 10: 22). Frequent HIV-1 integrase polymorphisms (e.g. L101I or T124A) have a minimal effect on dolutegravir susceptibility in phenotypic assays (Vavro et al. Antimicrob Agents Chemother 2013; 57: 1379-1384).

Secondary mutations such as M50I, H51Y, E138K or the polymorphism E157Q may appear in combination with R263K and increase resistance to dolutegravir [Mesplède et al. J Antimicrob Chemother 2014; 69: 2733-2740; Wainberg et al. J Int AIDS Soc 2014; 17 (suppl 3): 19518; Anstett et al. J Antimicrob Chemother 2016; 71: 2083-2088], although in the case of H51Y this increase is accompanied by a dramatic loss of enzymatic activity and viral replication capacity (Mesplède et al. Retrovirology 2013; 10: 22). However, M50I has a minimal impact on the viral replication capacity of the R263K mutant (Wares et al. Retrovirology 2014; 11: 7). R263K has a deleterious effect on HIV fitness that seems to be linked to the integration process. Prolonged infections with R263K-containing viruses lead to a gradual decrease in integrated DNA, without altering the levels of early and late reverse transcription products (Mesplède et al. mBio 2017; 8: e00157-17).

Other mutations associated with dolutegravir resistance occur at positions 118, 121 and 153. G118R and F121Y confer high level resistance to dolutegravir, raltegravir and elvitegravir in strains of HIV-1 subtypes CRF02_AG and B derived from patients treated with raltegravir and elvitegravir (Malet et al. J Antimicrob Chemother 2014; 69: 2118-2122). In the wild-type HIV-1_{NL4-3} strain, single-mutants G118R and F121Y produced a 5- to 10-fold increase in resistance to dolutegravir. It has been also reported that mutations in the vicinity of the 3´-polypurine tract (3´PPT) could also confer high-level resistance to dolutegravir and other IN strand transfer inhibitors (Malet et al. Conference on Retroviruses and Opportunistic Infections 2017, Seattle, USA, Abstract 499).

**RESISTANCE TO CABOTEGRAVIR (GSK 1265744, GSK 744) AND BICTEGRAVIR (GS-9883)**

Cabotegravir is a strand transfer inhibitor of HIV-1 integrase, with a carbamoyl pyridone structure similar to dolutegravir (Yoshinaga et al. Antimicrob Agents Chemother 2015; 59: 397-406). It can be administered as a long-acting parenteral nanosuspension
via intramuscular or subcutaneous infection. It has a half-life of 21-50 days under this presentation. It is currently being tested in phase II clinical trials as a maintenance therapy in combination with rilpivirine (Margolis et al. Lancet Infect Dis 2015; 15: 1145-1155). In those trials, cabotegravir showed a high barrier to resistance although the IN substitution Q148R was selected in one patient exposed to cabotegravir/rilpivirine.

Studies in vitro showed cabotegravir activity against raltegravir-resistant isolates. Mutant viruses containing the raltegravir-resistant Y143R, Q148K, N155H, and G140S/Q148H variants had less than 6.1-fold increased cabotegravir inhibitory activity relative to the wild-type virus, while increases of 10 to >100-fold were observed for raltegravir inhibition (Yoshinaga et al. Antimicrob Agents Chemother 2015; 59: 397-406). Amino acid substitutions T124A, S153Y and Q146L in the HIV-1 IN were selected after successive passages of the virus in presence of drug. Studies with SIV-infected macaques treated with cabotegravir revealed the presence of IN mutations E92G/Q and G118R in virus found in rectal and vaginal fluids after 8 weeks of treatment (Radzio et al. Conference on Retroviruses and Opportunistic Infections 2017, Seattle, USA, Abstract 84).

Bictegravir is a structurally similar HIV-1 IN strand transfer inhibitor that like dolutegravir showed high efficacy up to 24 weeks, in phase II clinical trials, when given in combination with the RT inhibitors emtricitabine and tenofovir alafenamide (Sax et al. Lancet HIV 2017; 4: e154-e160). Bictegravir has potent activity against raltegravir- and elvitegravir-resistant strains. Its resistance profile is similar to that of dolutegravir with IN amino acid substitutions M50I and R263K, being selected after successive passages of HIV-1 in the presence of drug (Tsiang et al. Antimicrob Agents Chemother 2016; 60: 7086-7097). Currently, it is being developed as a single tablet coformulated with RT inhibitors tenofovir alafenamide and emtricitabine. In clinical trials, resistance was not detected after 48 weeks of treatment (Paul et al. Conference on Retroviruses and Opportunistic Infections 2017, Seattle, USA, Abstract 41). In phenotypic assays, HIV-1 IN mutants Y143R, N155H, R263K, M50I/R263K, E138K/R263K, and G140S/Q148H remained susceptible to bictegravir (≤3-fold increase in the EC$_{50}$), but H51Y/R263K conferred low-level resistance to the drug (~8-fold) (Hassounah et al. Conference on Retroviruses and Opportunistic Infections 2017, Seattle, USA, Abstract 498).
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<tr>
<th>Amino acid substitution</th>
<th>In vivo / In vitro</th>
<th>Comments and references</th>
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<tbody>
<tr>
<td>L45Q L45V</td>
<td>In vitro</td>
<td>Suggested as minor changes with a phenotypic impact on the susceptibility to elvitegravir, in the absence of major resistance mutations (Garrido et al. Antimicrob Agents Chemother 2012; 56: 2873-2878).</td>
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<tr>
<td>A49P</td>
<td>In vivo</td>
<td>Implicated in an unusual mutational pathway leading to dolutegravir resistance, observed in a heavily-treated patient who previously developed the N155H mutation in response to raltegravir therapy (Hardy et al. J Antimicrob Chemother 2015; 70: 405-411).</td>
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<td>H51Y</td>
<td>In vitro</td>
<td>Confers low-level resistance to elvitegravir (Margot et al. Antiviral Res 2012; 93: 288-296), and enhances dolutegravir resistance mediated by the R263K mutation (Mesplède et al. Retrovirology 2013; 10: 22). The double-mutant H51Y/R263K shows 15-fold decreased susceptibility to dolutegravir, relative to the wild-type virus, but shows a significant reduction in its replication capacity. See also R262K.</td>
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<td>V54I</td>
<td>In vitro</td>
<td>Selected as a compensatory mutation in virus containing the Q148R mutation and grown in the presence of raltegravir (Goethals et al. Virology 2010; 402: 338-346).</td>
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<tr>
<td>T66I</td>
<td>In vivo</td>
<td>Primary resistance mutation emerging during treatment with QUAD (elvitegravir/cobicistat/emtricitabine/tenofovir) and showing cross-resistance to raltegravir [White et al. Antivir Ther 2012; 17 (suppl 1): A12].</td>
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<td>T97A</td>
<td>In vivo</td>
<td>Rarely-found polymorphism identified in elvitegravir-resistant HIV clones (Ceccherini-Silberstein et al. Antimicrob Agents Chemother 2010; 54: 3938-3948). In combination with Y143C/R, it has also been found in patients failing raltegravir-containing regimens (Reigadas et al. PLoS One 2010; 5: e10311).</td>
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<td></td>
<td>In vitro</td>
<td>In strand transfer assays carried out with recombinant IN, the T97A mutation produces a severe reduction of the susceptibility to raltegravir conferred by Y143C/R, while rescuing the catalytic defect due to the 143 mutation (Reigadas et al. Antimicrob Agents Chemother 2011; 55: 3187-3194). However, phenotypic studies with site-directed mutants and clinical isolates showed that it confers only low-level resistance to elvitegravir and raltegravir (Abram et al. Antimicrob Agents Chemother 2013; 57: 2654-2663; Abram et al. PLoS One 2017; 12: e0172206).</td>
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<td>Y99H</td>
<td>In vitro</td>
<td>Selected in the presence of BI-D, a non-catalytic IN inhibitor, together with mutations L102F, H171T and N222K [Fenwick et al. Antivir Ther 2011; 16 (suppl. 1): A9].</td>
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<td>S119G</td>
<td>In vitro</td>
<td>These natural polymorphisms have been associated with reduced replication capacity ex vivo (Brockman et al. J Virol 2012; 86: 6913-6923; Capel et al. Virology 2013; 444: 274-281). S119R has been identified as an escape mutation associated with a protective HLA-C*05 allele (Brockman et al. J Virol 2012; 86: 6913-6923). This polymorphism is frequently observed in combination with Q148H/R or N155H in treated patients and enhances the level of resistance to integrase strand transfer inhibitors produced by Y143C, Q148H or N155H. Other polymorphisms at this codon (e.g. S119G/P/T) do not have an impact on drug susceptibility (Hachiya et al. Antiviral Res 2015; 119: 84-88).</td>
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<td>T122I</td>
<td>In vivo</td>
<td>This polymorphism has been associated with poor virological response to raltegravir in a large European cohort [Armenia et al. Antivir Ther 2011; 16 (suppl. 1): A69].</td>
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<td>Y143A</td>
<td>In vitro</td>
<td>Their impact on raltegravir susceptibility is similar to that shown by Y143C. Usually, they require multiple secondary substitutions to develop large reductions in raltegravir susceptibility (Huang et al. Antimicrob Agents Chemother 2013; 57: 4105-4113). Patient-derived viruses containing Y143 substitutions exhibit cross-resistance to elvitegravir.</td>
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<td>P145S</td>
<td>In vivo</td>
<td>Selected in one patient treated with raltegravir, in the context of a clinical trial including 49 individuals (Gallien et al. AIDS 2011; 25: 665-669).</td>
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<td></td>
<td>In vitro</td>
<td>Appears together with other mutations (e.g. T66I, Q95K and Q146P, or H51Y, E92Q and E157Q) in viral isolates selected in vitro with elvitegravir (Shimura et al. J Virol 2008; 82: 764-774). Confers 9.5-fold increased resistance to elvitegravir, but has no effect on raltegravir resistance (Margot et al. Antiviral Res 2012; 93: 288-296).</td>
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<td><strong>Q148N</strong></td>
<td><strong>In vitro</strong></td>
<td>Q148N alone or in combination with G140S confers 2.4-4.5-fold reduced susceptibility to elvitegravir depending on the viral genetic context, but had no effect on resistance to raltegravir and dolutegravir (Varghese et al. AIDS Res Hum Retroviruses 2016; 32: 702-704).</td>
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<td><strong>I151L</strong></td>
<td><strong>In vitro</strong></td>
<td>It confers resistance to L-870,810, S-1360 and elvitegravir (Kobayashi et al. Antiviral Res 2008; 80: 213-222).</td>
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<td><strong>V151A</strong></td>
<td><strong>In vitro</strong></td>
<td>Selected with GS-278012, an analogue of GS-9160. Confers some resistance to elvitegravir and enhances resistance to various IN inhibitors when mutations E92Q or E92Q/G140S are present (Jones et al. Antimicrob Agents Chemother 2009; 53: 1194-1203).</td>
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<td>M154I</td>
<td>In vivo</td>
<td>Polymorphism found at a frequency of 6% in untreated patients and 21.3% in antiretroviral-treated patients (Ceccherini-Silberstein et al. J Antimicrob Chemother 2010; 65: 2305-2318).</td>
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<td>M154L</td>
<td>In vivo</td>
<td>Absent in naïve patients, reaches a prevalence of 5.7% in treated patients. This mutation is positively associated with the RT resistance mutations F227L and T215Y (Ceccherini-Silberstein et al. J Antimicrob Chemother 2010; 65: 2305-2318).</td>
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<td>G163E</td>
<td>In vivo</td>
<td>Selected after 20 days on therapy in one patient with a high viral load, who initiated treatment with tenofovir disoproxil fumarate/emtricitabine plus dolutegravir. Its significance is uncertain (Fulcher et al. Conference on Retroviruses and Opportunistic Infections 2017, Seattle, USA, Abstract 500).</td>
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<td>V165I</td>
<td>In vitro</td>
<td>See T124N.</td>
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<td>H171T</td>
<td>In vitro</td>
<td>Major mutation associated with resistance to BI-D, a non-catalytic IN inhibitor. It has been selected in vitro together with Y99H, L102F and N222K [Fenwick et al. Antivir Ther 2011; 16 (suppl. 1): A9]. Virus containing the H171T substitution showed around 68-fold resistance to BI-D, despite affecting only modestly IN-LEDGF/p75 binding (Slaughter et al. Retrovirology 2014; 11: 100).</td>
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<td>T174I</td>
<td>In vitro</td>
<td>Associated with resistance to non-catalytic site IN inhibitors, such as KF116 (see T124N) and GS-9695 (Mitchell et al. Conference on Retroviruses and Opportunistic Infections 2017, Seattle, USA. Abstract 434).</td>
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<td>S230R</td>
<td>In vitro</td>
<td>Appears together with T66I and L74M in virus isolated in the presence of L-708,906 (Fikkert et al. J Virol 2003; 77: 11459-11470). These variants were also resistant to S-1360 (Fikkert et al. AIDS 2004; 18: 2019-2028), but were susceptible to V-165 (Fikkert et al. J Virol 2003; 77: 11459-11470).</td>
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<td>L234V</td>
<td>In vitro</td>
<td>Implicated in a rare mutational pathway leading to dolutegravir resistance, observed in a heavily-treated patient who previously developed the N155H mutation in response to raltegravir therapy (Hardy et al. J Antimicrob Chemother 2015; 70: 405-411).</td>
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<td>R262K</td>
<td>In vitro</td>
<td>Found together with H51Y in virus selected <em>in vitro</em> with dolutegravir. The combination of both substitutions had a modest effect on dolutegravir susceptibility (Cutillas et al. Antimicrob Agents Chemother 2015; 59: 310-316).</td>
</tr>
<tr>
<td>Amino acid substitution</td>
<td>In vivo / In vitro</td>
<td>Comments and references</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>R263K</td>
<td><em>In vivo</em></td>
<td>Developed in patients infected with HIV-1 group M subtypes B and C treated with dolutegravir in clinical trials, but conferred low levels of resistance to the drug (Cahn et al. Lancet 2013; 382: 700-708).</td>
</tr>
<tr>
<td></td>
<td><em>In vitro</em></td>
<td>Confers low-level resistance to elvitegravir (Margot et al. Antiviral Res 2012; 93: 288-296; Garrido et al. Antimicrob Agents Chemother 2012; 56: 2873-2878). In addition, R263K was the most common mutation emerging in selection experiments carried out in the presence of dolutegravir with viruses of subtypes B, C and A/G. This mutation produces an 11.2-fold increase in the IC\textsubscript{50} for dolutegravir in comparison with that obtained with wild-type HIV-1\textsubscript{NL4-3} (Quashie et al. J Virol 2012; 86: 2696-2705), although reported increases of the IC\textsubscript{50} seem to be smaller when assayed with the PhenoSense® Integrase assay (Mesplède et al. Retrovirology 2013; 10: 22). R263K delays the emergence of resistance against raltegravir, but the presence of secondary mutations such as H51Y or E138K mitigates this inhibitory effect (Oliveira et al. AIDS 2015; 29: 2255-2260). The R263K substitution in HIV-1 subtype C is more deleterious for IN enzymatic function and viral replication than in subtype B (Mesplède et al. AIDS 2015; 29: 1459-1466). It was also selected <em>in vitro</em> after exposure to increasing concentrations of bictegravir (GS-9883), usually in combination with M50I (Tsiang et al. Antimicrob Agents Chemother 2016; 60: 7086-7097).</td>
</tr>
</tbody>
</table>
Figure 5.3. Summary of phenotypic drug susceptibility data obtained from relevant mutations and combinations of amino acid substitutions in the HIV-1 IN, involved in resistance to IN inhibitors. High-level (>100-fold increase of the IC$_{50}$ for the inhibitor), moderate (10- to 100-fold increase) and low-level (3- to 10-fold increase) resistance are represented by solid, hatched and grey boxes, respectively. Open boxes indicate susceptible viruses (<3-fold increase in the IC$_{50}$ for the inhibitor). Data shown have been taken from Kobayashi et al. Antiviral Res 2008; 80: 213-222; Shimura et al. J Virol 2008; 82: 764-774; Fransen et al. J Virol 2009; 83: 11440-11446; Jones et al. Antimicrob
Table 5.2. OVERVIEW OF GENOTYPIC RESISTANCE TO INTEGRASE INHIBITORS

<table>
<thead>
<tr>
<th>Integrase inhibitor</th>
<th>Selection process</th>
<th>Integrase mutations</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir (GS-9883)</td>
<td><em>In vitro</em></td>
<td>M50I, R263K</td>
<td>1</td>
</tr>
<tr>
<td>Dolutegravir (S/GSK1349572)</td>
<td><em>In vitro</em></td>
<td>R263K; M50I/R263K; H51Y/R263K; E138K/R263K</td>
<td>3-5</td>
</tr>
<tr>
<td></td>
<td><em>In vitro</em></td>
<td>E92Q/G193E; Q148K/R/H (± E138K, G140S, T97A)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T97A/Y143C; G140S/Q148R; G140T/Q148R/N155H (in HIV-2)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>In patients</td>
<td>R263K</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>In patients</td>
<td>G118R (± E138K), F121Y</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>In patients</td>
<td>G118R, Q148R/H, N155H</td>
<td>10</td>
</tr>
<tr>
<td>Cabotegravir (GSK1265744, GSK744)</td>
<td>In patients</td>
<td>Q148R</td>
<td>11</td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td>Selection process</td>
<td>Integrase mutations</td>
<td>Refs.</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>------</td>
</tr>
<tr>
<td>Elvitegravir (GS-9137)</td>
<td><em>In vitro</em></td>
<td>E92Q (+ H51Y, S147G, and E157Q)</td>
<td>12, 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T66I (+ R263K or + S153Y and F121Y)</td>
<td>12, 14</td>
</tr>
<tr>
<td></td>
<td><em>In patients</em></td>
<td>T66A/K E92Q (+ N155H) Q148R (+E138A/K or +G140C/S or +S147G) N155H</td>
<td>15</td>
</tr>
<tr>
<td>GS-9160</td>
<td><em>In vitro</em></td>
<td>L74M/E92V</td>
<td>16</td>
</tr>
<tr>
<td>L-708,906</td>
<td><em>In vitro</em></td>
<td>T66I/M154I</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T66I/S153Y</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N155S</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T66I/L74M/S230R</td>
<td>19</td>
</tr>
<tr>
<td>L-870,810</td>
<td><em>In vitro</em></td>
<td>V72I/F121Y/T125K/V151I</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L74M/E92Q/S230N</td>
<td>20</td>
</tr>
<tr>
<td>MK-2048</td>
<td><em>In vitro</em></td>
<td>G118R/E138K</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N155H</td>
<td>22</td>
</tr>
<tr>
<td>Raltegravir (MK-0518)</td>
<td><em>In vitro</em></td>
<td>E138A/G140A/Q148K</td>
<td>23</td>
</tr>
<tr>
<td>S-1360</td>
<td><em>In vitro</em></td>
<td>T66I/L74M/A128T/E138K/Q146K/S153A</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K160D/V165I/V201I</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T66I/T124A/N155S</td>
<td>30</td>
</tr>
</tbody>
</table>

a Resistance genetic pathways in HIV-2 include mutations E92Q/Y143R/N155H, T97A/Y143C, T97A/N155H, G140S/Q148R, Q148K and Q148R (Charpentier et al. 393


References: