Table 251.1. Mean activity of dolutegravir against HIV-1 subtypes and HIV-2.

| Virus | Cell type used for assay | Mean $IC_{50}$ (nM) |
|---|---|---|
| HIV-1, subtype A | PBMCs | 0.26 |
| HIV-1, subtype B | PBMCs | 0.62 |
| HIV-1, subtype C | PBMCs | 0.23 |
| HIV-1, subtype D | PBMCs | 0.23 |
| HIV-1, subtype E | PBMCs | 0.22 |
| HIV-1, subtype F | PBMCs | 0.25 |
| HIV-1, subtype G | PBMCs | 0.36 |
| HIV-1, group O | PBMCs | 0.87 |
| HIV-2 | PBMCs | 0.29 |
| HIV-1, subtype B | Macrophages | 1.07 |

*Abbreviations*: $IC_{50}$: 50% inhibitory concentration; PBMCs: peripheral blood mononuclear cells.
*Source:* ViiV, data on file.

(Charpentier *et al.*, 2013), the median $EC_{50}$ value was 1.22 nM (range: 0.08–3.72 nM), and for an additional 9 HIV-2 isolates (Charpentier *et al.*, 2010) the dolutegravir median $EC_{50}$ was 0.8 nM (range: 0.2–1.4 nM).

### NON-HIV VIRUSES

Dolutegravir was evaluated for antiviral activity against a panel of 19 non-HIV viruses (ViiV, data on file). Dolutegravir caused a mild cytotoxic effect at the high test concentration of 100 μM. In general, dolutegravir did not exhibit measureable antiviral activity ($EC_{50}$ < 100 μM) in this panel for adenovirus, yellow fever virus, HSV-1, HSV-2, influenza A, influenza B, human parainfluenza, respiratory syncytial virus, coxsackie A virus, coxsackie B virus, enterovirus, polio virus, rhinovirus, and human cytomegalovirus. Some low-level inhibitory activity was observed against bovine viral diarrhea virus ($EC_{50}$ = 66 μM), dengue virus (serotype 2) ($EC_{50}$ = 69.5 μM), measles virus (morbillivirus) ($EC_{50}$ = 30.3 μM), hepatitis C virus (replicon assay; $EC_{50}$ = 11.2 μM), and varicella zoster virus (plaque reduction assay; $EC_{50}$ = 88.1 μM).

## 2b. Emerging resistance and cross-resistance

Resistant mutants have been isolated during passage of wild-type HIV or HIV with raltegravir resistance mutations and during passage of HIV-1 subtypes B, A/G, and C in the presence of dolutegravir.

When HIV-1 IIIB was passaged in the presence of dolutegravir for 112 days, viruses with a 4.1-fold maximum increase in $EC_{50}$ and S153Y or S153F substitutions in integrase polymorphic sites were observed (Kobayashi *et al.*, 2011). Passage of the wild-type HIV-1 NL432 in the presence of 6.4 nM dolutegravir selected for E92Q (fold change = 3.1) and G193E (fold change = 3.2) substitutions in the integrase region (Sato *et al.*, 2009). Passage of HIV-1 subtypes B and A/G in TZM-bl cells selected for IN mutation R263K (Quashie *et al.*, 2012; Oliveira *et al.*, 2012). Passage of HIV-1 NL432 with Q148H, Q148K, or Q148R raltegravir-resistant mutations resulted in selection of additional mutations and an increase in dolutegravir fold change; passage of HIV-1 NL432 with E92Q, Y143C, Y143R, or N155H raltegravir-resistant mutations did not lead to additional substitutions (Seki *et al.*, 2015).

Comparative susceptibilities to dolutegravir and raltegravir were obtained from 60 raltegravir-resistant site-directed HIV-1 mutants and 6 site-directed HIV-2 mutants. Dolutegravir retained activity against a vast majority of these mutants (Kobayashi *et al.*, 2011). In addition, susceptibilities to dolutegravir and raltegravir were determined for more than 705 raltegravir-resistant clinical isolates, with dolutegravir retaining activity (< 10-fold change) against > 90% of them (Underwood *et al.*, 2013). Dolutegravir has a < 10-fold change against 67 (73%) of the 92 clinical isolates with Q148 plus at least two INSTI resistance substitutions and 168 (91%) of the 184 isolates with Q148 plus one INSTI resistance substitution.

Virologic findings from studies conducted under the dolutegravir clinical program show that dolutegravir 50 mg once daily has a relatively high barrier to resistance in INSTI-naive patients. This has been demonstrated in a treatment-experienced, INSTI-naive population in the ING111762/SAILING study (Cahn *et al.*, 2013) where statistically significantly fewer virologic failures and statistically significantly fewer subjects with INSTI resistance (in addition to less treatment-emergent resistance to the background regimens) were observed when compared with raltegravir (INSTI-resistant patient data are discussed in section 5c, Clinically important pharmacokinetic and pharmacodynamic features). Data from phase III studies ING113086/SPRING-2 and ING114467/SINGLE, which include > 1600 treatment-naive patients are also supportive of dolutegravir's relatively high barrier to resistance, given that no subjects on the dolutegravir regimen developed resistance to either dolutegravir or the background nucleos(t)ide reverse transcriptase inhibitors (NRTIs), whereas resistance to both the third agent and the background NRTIs was observed in both the raltegravir- and efavirenz-based comparator arms. Recent data suggest that the M184I/V and K65R mutations prevent the emergence of resistance to dolutegravir, but not to raltegravir or elvitegravir (Oliveira *et al.*, 2016).

A unique integrase substitution was observed (R263K or R263R/K mixture) in two subjects on dolutegravir with protocol-defined virologic failure in the SAILING study (Cahn *et al.*, 2013); these conferred no or low-fold change in susceptibility to dolutegravir and to raltegravir. The R263K mutation has been selected during passage with elvitegravir (Jones *et al.*, 2007), has been infrequently observed during raltegravir therapy (Brenner *et al.*, 2011), and most recently was selected during *in vitro* passage with dolutegravir (Quashie *et al.*, 2012; Oliveira *et al.*, 2012). Alternatively, a G118R substitution was selected with dolutegravir in tissue culture (Quashie *et al.*, 2012). Both these mutations confer a relatively low resistance level and decrease integrase enzyme