Rational Design of Doravirine (DOR): A Review of Development From Bench to Patients

**BRIEF HISTORY OF THE NNRTI CLASS**
- **Early/mid 1990s:** discovery of first NNRTIs: 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine
- **Resistance profiling studies with DOR and related analogs demonstrated that they were less effective**

**STRUCTURE-BASED DRUG DESIGN WAS CRUCIAL TO RESISTANCE PROFILING**
- **DOR discovery effort started from a screen of 100,000 compounds by Merck (MMV) in the mid-1990s.**
- **Resistant profiling studies with DOR and related analogs demonstrated that they were less effective**
- **DOR efficiency (5.09) was lower than expected but was superior to other NNRTIs in studies comparing NNRTIs to PIs.**

**PREREQUISITE ADOPTION OF NNRTI-RESISTANT VIRUSES**
- **Early identification of NNRTI-resistant virus was crucial**
- **DOR efficiency (5.09) was lower than expected but was superior to other NNRTIs in studies comparing NNRTIs to PIs.**

**CLINICAL TRIAL OBSERVATIONS**
- **First phase 3 trial: DOR vs EFV and RPV in treatment-naive patients**
- **DOR efficacy (83.8%; 95% CI: 79.0 to 87.4) vs DRV+r (79.9%; 95% CI: 75.3 to 83.5)**
- **Neuropsychiatric AEs**
  - **DOR vs EFV in treatment-experienced patients**
  - **DOR vs DRV+r in treatment-experienced patients**
- **DOR efficiency (5.29) was better than expected but was superior to other NNRTIs in studies comparing NNRTIs to PIs.**

**SAFETY AND TOLERABILITY**
- **Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has recently**
- **DOR has a unique PK profile compared to other NNRTIs**
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**CONCLUSIONS**
- **Two decades of research on NNRTIs**
- **Numerous failures but wealth of preclinical and clinical experience**
- **Helped to build a logical, step-by-step approach to NNRT development that addressed novelty**

**References**