54.5. Rational Design of Doravirine (DOR): A Review of Development From Bench to Patients
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Session: 60. HIV: Antiretroviral Therapy
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Background. First-generation NNRTIs with nucleoside reverse transcriptase inhibitors are effective in sustaining HIV-1 suppression but development of resistant mutants is often seen in patients whose regimens fail. These NNRTIs are also associated with safety/tolerability issues, such as CNS and rash. Despite intensive efforts in developing NNRTIs with improved resistance and safety profiles, only two next-generation NNRTIs were successfully developed over the last decade, etravirine (ETR) and rilpivirine (RPV). RPV is less efficacious in patients with high viral load and ETR is only approved for treating experienced patients. Lessons from the limitations of approved NNRTIs and past development failures informed a rational approach to the development of DOR.

Methods. This review describes the development of DOR, which applied resistance selection and crystallography studies to improve resistance profiles, qEUG studies to evaluate CNS effects, and animal studies to optimize pharmacokinetic profiles, with confirmation in clinical trials.

Results. DOR demonstrated potent in vitro activity against wild-type virus and mutant viruses containing common NNRTI resistance mutations (K103N, Y181C, G190A, E138K, and K103N/Y181C), and selection studies suggested a unique resistance profile characterized by the emergence of a mutation at position 106 (V106A/M) with additional substitutions, such as F227C, required for high-level resistance. Related analogs were devoid of qEUG effects in rats and nonhuman primates. The metabolic profile of DOR was devoid of induction potential, suggesting a benign drug interaction profile. In the ongoing clinical studies, resistance rates were lower than first-generation NNRTIs, with no clinically meaningful drug interactions, and DOR has been generally well tolerated with favorable safety, neurophysiologic, and lipid profiles.

Conclusion. Clinical experience confirmed the preclinical profile of DOR. DOR is a unique NNRTI, distinguished by its low risk of resistance and excellent tolerability. DOR demonstrated a superior neuropsychiatric profile compared with EFV, a superior lipid profile vs. DRV+EFV, and a favorable drug–drug interaction profile compared to other integrase transfer inhibitors.

Disclosures. C. Hwang, Merck & Co., Inc.; Employee and Shareholder, Salary. M. T. Lai, Merck & Co., Inc.; Employee and Shareholder, Salary. D. Hazuda, Merck & Co., Inc.; Employee and Shareholder, Salary.

54.6. No Difference in MK-8591 and Doravirine Pharmacokinetics After Co-Administration
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Background. MK-8591 is a novel, highly potent, nucleoside reverse transcriptase transcriptional activator inhibitor (NRTTI) that is in development for the treatment of HIV-1 infection. MK-8591 is not expected to be a perpetrator or victim of drug–drug interactions (DDI), as it does not interact with renal or hepatic transporters, or with cytochrome P450 (CYP) enzymes in vitro. Doravirine (DOR), a novel non-nucleoside reverse transcriptase inhibitor (NNRTI), does not interact significantly with hepatic transporters or CYP enzymes but is metabolized by CYP3A4 in vitro. As MK-8591 is neither an inducer nor an inhibitor of CYP3A4, an interaction between MK-8591 and DOR was not expected. Currently, MK-8591 is being evaluated in a Phase 2 trial in combination with DOR.

Methods. The two-way interaction between MK-8591 and DOR was investigated in a double-blind, placebo-controlled, randomized, fixed-sequence, two-way drug–drug interaction study in 14 healthy adult subjects. Subjects received 5 days of 100 mg DOR or placebo QD, followed by 19 days of 2.25 mg MK-8591 or placebo QD, with 100 mg DOR or placebo co-administered QD for the last 5 days. Ten subjects received active drug and four received placebo throughout the trial.

Results. Multiple daily doses of MK-8591 and DOR alone and in combination were generally well tolerated. As noted in the table, the DOR area under the curve from time zero to 24 hours (AUC(0-24), concentrations (C24), and maximum concentration (Cmax) were similar with and without MK-8591, and the MK-8591 AUC0-24 and Cmax were similar with and without DOR.

Table: Geometric Mean Ratio (GMR) with 90% Confidence Interval, Relative to Single Agent Administration (N = 10)

|        | DOR       | MK-8591 |
|--------|-----------|---------|
| MK-8591| 1.13 (1.01, 1.28) | 1.06 (1.01, 1.12) |
| C24    | 1.12 (0.95, 1.32) | 1.08 (0.91, 1.27) |

Conclusion. No clinically significant differences in PK were observed when MK-8591 and DOR were co-administered, which supports the Phase 2 co-dosing of MK-8591 and DOR. Consistent across trials, MK-8591 does not appear to interact with CYP3A4-mediated metabolism.

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54.7. Results of Patient-Reported Outcome Data From the Phase III BRIGHTE Study of Fostemsavir
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Background. The Phase 3 BRIGHTE study evaluated fostemsavir in heavily treatment-experienced HIV-1 patients failing their current antiretroviral (ARB) regimen and unable to construct a viable regimen from remaining available agents. Week 24 efficacy and safety have been previously reported—fostemsavir resulted in virologic and immunological improvements and was generally well tolerated. The objective of this abstract is to report analyses of patient-reported outcomes (PROs) from BRIGHTE.

Methods. BRIGHTE included two cohorts: the randomized cohort (RC) had one to two classes of ARV therapy available; the non-randomized cohort (NRC) had no ARV classes available. RC patients received fostemsavir or placebo + existing failing regimen for 8 days, and thereafter fostemsavir + optimized background therapy (OBT); NRC received fostemsavir + OBT throughout. PROs included the Functional Assessment of HIV Infection (FAHI), the EuroQol-5D-3L (EQ-5D) and associated visual analogue scale (VAS).

Results. Both cohorts had advanced disease, low CD4 counts (median of 99.5 in RC and 41 in NRC) and high proportions of patients with AIDS (84% in RC and 90% in NRC). This was reflected in fairly low baseline FAHI scores. Improvements from baseline to Week 24 were observed in FAHI total score, physical well-being and emotional well-being subscales, with limited/no change in function/global well-being, social well-being and cognitive function. Improvements in the RC were close to published values for minimum clinically important differences, with smaller improvements in the NRC. EQ-5D utilities were similar at Week 24 to baseline in both cohorts, with improvements in the EQ-5D VAS (11% in the RC, 8% in the NRC).

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reviewed. ART regimens were assigned the following designations: contemporary first-line, contemporary non-first-line, older three-drug, two-drug, salvage, or off-ART. ART was also categorized as boosted (containing cobicistat/ritonavir) vs. unboosted, by single-tablet regimen (STR) vs. multi-tablet regimen (MTR), and frequency of dosing. Correlations between ART regimen, viral suppression, and age were analyzed.

Results. The ART review included 1,215 individuals. Most patients (68%) were on contemporary first-line regimens; 20% were on contemporary non-first-line regimens (figure). Patients on salvage regimens had lower rates of viral suppression than those in other ART categories (80% vs. 90%, P < 0.05). Most patients (90%) were prescribed once daily regimens and of those, 39% were prescribed STRs. There were no significant associations between viral suppression and regimen complexity (P = 0.8). There were 447 (37%) patients on boosting agents with no difference in viral suppression rate (88% suppressed on boosted regimens vs. 90% on unboosted, P = 0.3).

Conclusion. In a US urban, safety-net clinic, most patients were on contemporary ART regimens and 90% were on once-daily therapy. Despite these encouraging findings, systematic review identified many patients that could be considered for modernization and simplification with intent to minimize toxicity, side-effects, drug interactions, and cost.

Clinic Wide ART Regimen by ART Category

Disclosures. All authors: No reported disclosures.

549. Weight and BMI Changes in HIV-Infected Virologically Suppressed Adults after Switching to an Elvitegravir- or Dolutegravir-Containing Regimen

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Background. Use of integrase inhibitors (INIs) has increased in the management of HIV infection, with clinical efficacy and less frequent resistance. This study describes the weight and BMI changes in adults who switched to an elvitegravir- or dolutegravir-containing regimen.

Methods. This retrospective observational study evaluated weight and BMI changes in non-inferior HIV-infected patients who switched to an elvitegravir- or dolutegravir-containing regimen. Patients ≥18 years old on a stable ART regimen seen at the University of Utah Health Infectious Diseases Clinic between January 1, 2012 and February 28, 2017 who switched to an elvitegravir- or dolutegravir-containing regimen for at least 1 year were included. Exclusion criteria included patients with hypogonadism, or a thyroid disorder, patients who received medications that impact weight (including steroids, levomethyline, and metformin), and patients with two consecutive HIV viral load values >200 copies/mL during the study period. Body weight and BMI values collected prior to and ~1 year after the switch date were compared using paired t-tests. Data were collected for HIV-infected patients in care at six US-based HIV treatment centers. Patients eligible for the study initiated their first ART between January 2015 and December 2016. First ART regimen was assigned based on absence of prior ART prescriptions and a 30-day pre-treatment period with no ART dispensed or for less than 7 days. If ART included efavirenz, a high baseline viral load (>100,000) was defined. Baseline BMI was assessed using proportion of days covered (PDC). Follow-up was ≥265 days with duration capped at 365 days for consistency comparisons.

Results. A total of 1,499 patients met the criteria for the study: 66% (982/1,499) received STR and 34% (517/1,499) MTR. Top STRs were EVG/c/TAF/FTC (250/982, 26%), EVG/c/TDF/FTC (265/982, 27%), DRV + RTV + TDF/FTC (69/517, 13%), DRV + TDF/FTC (60/517, 12%), and DRV/c + TDF/FTC (40/517, 8%). Average persistency for STRs was significantly longer than MTRs (p < 0.001). Average PDCs for STRs (P = 0.002). Average PDCs for MTRs were significantly higher for STRs at 91% vs. 83% for MTRs (P < 0.001). Within the STR group, older age was significantly associated with greater adherence (average age: 45 in 80%+ adherent group vs. 42 in <80% adherent group, P = 0.012). In both the STR and MTR groups, the percent of patients with weight gain >5% of baseline weight was assessed using proportion of days covered (PDC). Follow-up was ≥265 days with duration capped at 365 days for consistency comparisons.

Conclusion. This study of adherence with STR vs. MTR HIV therapy is novel, as it reviews currently used regimens and was conducted utilizing EMR, pharmacy dispensing data, and medical claims data limited to EFV-based therapies. In this study, we utilized EMR, prescription, and pharmacy dispensing data to assess STR and MTR adherence and persistency as observed in a network of clinical practices.

Disclosures. A. Mills, Viiv Healthcare; R. Priest, Viiv Healthcare; C. Jamjian, University of Utah Health, Salt Lake City, Utah; B. Allgood, University of Utah Health, Salt Lake City, Utah.

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