

## POSTER 9

### MECHANISM OF ACTION AND RESISTANCE TO PME0-5-METHYL-DAPy, A NOVEL PYRIMIDINE NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR

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6-[2-(phosphonomethoxy)ethoxy]-5-methyl-2,4-diaminopyrimidine (PME0-5-Me-DAPy) is a novel acyclic nucleotide reverse transcriptase (RT) inhibitor (NtRTI) that exhibits potent activity against wild-type (WT) and drug-resistant HIV-1. In this study, we have used transient and steady-state kinetic analyses to characterize the mechanisms by which PME0-5-Me-DAPy diphosphate (PME0-5-Me-DAPy-pp) inhibits recombinant purified WT or mutant (K65R, K70E, M41L/L210W/T215F, D67N/K70R/T215F/K219Q) HIV-1 RT. Although PME0-5-Me-DAPy-pp is a pyrimidine analog, it base-pairs with thymine (in DNA templates) or uracil (in RNA templates) and is incorporated, accordingly, as a purine analog. PME0-5-Me-DAPy-pp is not as efficiently incorporated by WT RT as tenofovir-pp and adefovir-pp (both of which are acyclic purine NtRTIs). However, PME0-5-Me-DAPy-pp acts as a better substrate for RT containing the K65R mutation in comparison with tenofovir-pp. Additional studies demonstrated that PME0-5-Me-DAPy-monophosphate is as efficiently excised by M41L/L210W/T215F RT or D67N/K70R/T215F/K219Q RT as tenofovir-monophosphate or adefovir-monophosphate, but is 2-fold more susceptible to dead-end complex formation. Taken together, these data show that a pyrimidine analog can be recognized as a purine by HIV-1 RT, suggesting that the nature of NtRTI base structure may influence the mechanism of action and resistance.