CROI 2017
Seattle, WA

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Antiviral Activity of EFdA Against NRTI-Sensitive and -Resistant Strains of HIV-2

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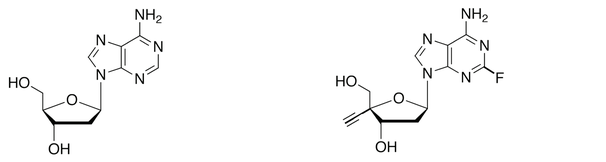
Background

HIV-2 infection is a significant public health problem in West Africa and has been reported in other countries with ties to the region.

Historically, clinical outcomes of antiretroviral therapy in HIV-2 and HIV-1/HIV-2 dually-positive patients have been poor, with high rates of immunovirologic failure and multidrug resistance. Newer antivirals with improved safety, efficacy, and resistance profiles are needed for HIV-2–infected individuals.

EFdA is a novel, 4´-modified nucleoside analog inhibitor



dA
(2´-deoxyadenosine)

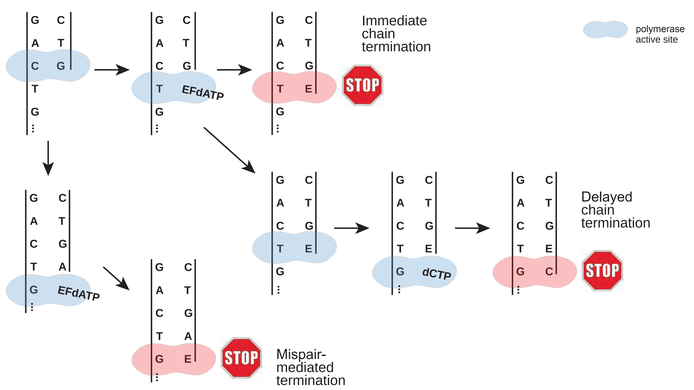
EFdA (MK-8591)
(4´-ethynyl-2-fluoro-2´-deoxyadenosine)

PubChem CID: 6483431

EFdA is a nucleoside reverse transcriptase translocation inhibitor (NRTTI). It is highly active against HIV-1 in culture, with EC_{50} values in the low-nanomolar to picomolar range and negligible cytotoxicity.

EFdA is converted to EFdA-5´-triphosphate (EFdATP) by cellular kinases and binds to the polymerase active site of HIV-1 reverse transcriptase (RT) with an affinity ≥ that of dATP.

EFdA inhibits HIV-1 RT via multiple mechanisms



Adopted from Michailidis et al., J. Biol. Chem. 289(35):24533

CLINICAL STUDIES

A single 10-mg dose of EFdA demonstrated potent antiviral activity for 10 days in a phase 1b proof-of-concept clinical trial.

Median plasma viral load reduction through d10 = 1.78 Log_{10} copies/ml.

Median half life of EFdA in plasma = 60 h.

Friedman et al., CROI 2016 Abstr. 437 LB

Efforts to evaluate the activity of EFdA against HIV-2 in culture are limited; a single report showed that a group B strain ($HIV\text{-}2_{EHO}$) was sensitive to the drug in spreading infections of MT-4 cells*. The ability of EFdA to inhibit HIV-2 mutants that are resistant to other NRTI is unknown.

* Kawamoto et al., Int. J. Biochem. Cell Biol. 40:2410

Aim

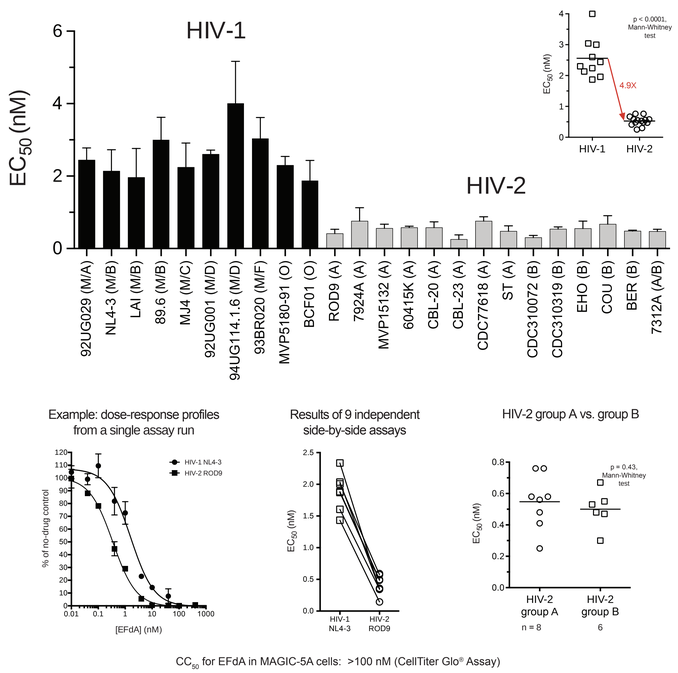
To evaluate the activity of EFdA against HIV-2 isolates and NRTI-resistant HIV-2 mutants in culture.

Approach

- Single-cycle drug susceptibility assays using HeLa-CD4 indicator cells (MAGIC-5A) and a colorimetric readout for quantifying viral infection (CPRG substrate conversion).
- Resistance testing with site-directed and patient-derived RT mutants.

Results

HIV-2 is more sensitive than HIV-1 to EFdA



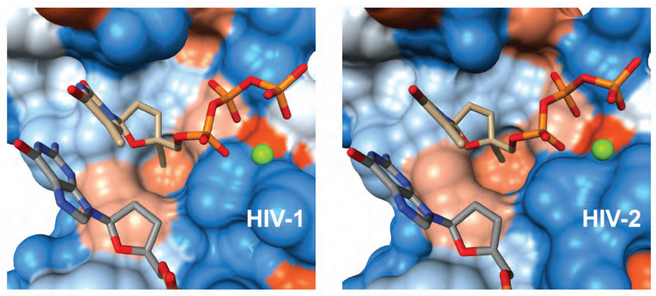
Example: dose-response profiles from a single assay run

Results of 9 independent side-by-side assays

HIV-2 group A vs. group B

CC_{50} for EFdA in MAGIC-5A cells: >100 nM (CellTiter Glo® Assay)

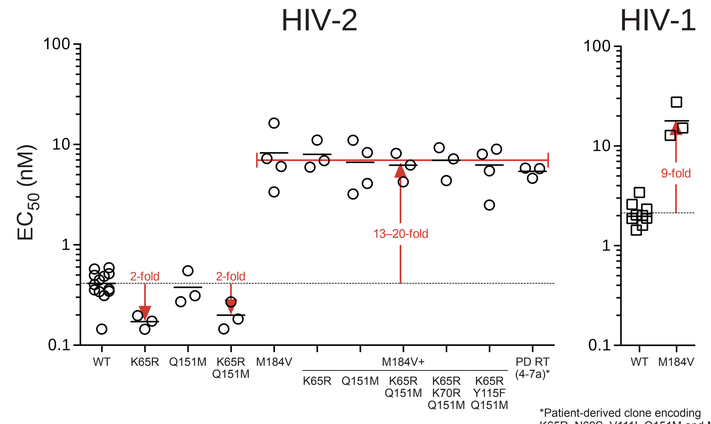
HIV-1 and HIV-2 RTs show subtle differences in the area surrounding the 4´-ethynyl group



2´,3´-didehydro-3´-deoxy-4´-ethynylthymidine is shown as the incoming nucleotide (Smith et al. Antimicrob. Agents Chemother. 59:7437).

Results

EFdA is active against NRTI-resistant HIV-2 mutants



*Patient-derived clone encoding K65R, N69S, V111I, Q151M and M184V.

Summary: EFdA resistance profile for HIV-2

Mutant	Fold Resistance to: AZT	FTC	EFdA	TDF*
K65R	1	85	0.4	1
Q151M	43	5	0.9	0.3
K65R+Q151M	56	250	0.5	2
M184V	1	>200	20	1
Q151M+M184V	29	>200	16	1
K65R+Q151M+M184V	66	>200	15	3
K65R+K70R+Q151M+M184V	116	>100	17	2
K65R+Y115F+Q151M+M184V	139	>100	15	4

*Values for single and double mutants were obtained using unmodified tenofovir.

Data for AZT, FTC and TDF are from Smith et al. J. Infect. Dis. 199:1323 and unpublished results.

Conclusions

EFdA a potent inhibitor of HIV-1 and HIV-2 in cell culture with mean EC_{50} values of 2.6 ± 0.6 nM and 0.53 ± 0.15 nM, respectively. The observation that HIV-2 is 5-fold more sensitive to EFdA can be explained by structural features that affect the 4'-ethynyl group.

As observed for HIV-1, K65R mutants of $HIV\text{-}2_{ROD9}$ are hypersusceptible to EFdA. K65R+Q151M mutants of HIV-2 are also hypersusceptible to the drug.

The M184V change in $HIV\text{-}2_{ROD9}$ confers a 20-fold shift in the potency of EFdA, but the EC_{50} for the mutant virus is only 3-fold higher than the mean EC_{50} for HIV-1. Addition of other NRTI resistance changes in combination with M184V does not increase the level of EFdA resistance in HIV-2.

EFdA should be further evaluated in clinical studies involving HIV-2–infected individuals.

Acknowledgments

We thank Merck & Co., Inc. for providing EFdA (MK-8591). VW recieved a monetary award for this project from the Mary Gates Undergraduate Research Program. These studies were also supported by grants to GSG from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID; AI060466 & AI120765) and the University of Washington Center for AIDS Research. The UW-Dakar HIV-2 Study Group includes Moussa Seydi,Papa Salif Sow, Selly Ba, Fatima Sall, Fatou Traore, Khadim Faye, Ousseynou Ndiaye, Marie Pierre Sy, Bintou Diaw, Mbaye Ndoye, Amadou Bale Diop, Marianne Fadam Diome (Service des Maladies Infectieuses Ibrahima Diop Mar, Centre Hospitalier Universitaire de Fann, Universite Cheikh Anta Diop de Dakar, Dakar, Senegal); Alas-sane Niang, El Hadji Ibrahima Sall, Ousseynou Cisse, Ibrahima Tito Tamba, Jean Phillippe Diatta, Raphael Bakhoum, Jacque Francois Sambou, Juliette Gomis (Region Medicale de Ziguinchor, Ziguinchor, Casamance, Senegal); Stephen Hawes, Noelle Benzekri, Robert Coombs, Ming Chang, John Lin, Nancy Kiviat, and James Mullins (Univ. of Washington).