Which Preclinical Species Mimics Tissue Penetration of Antiretroviral Drugs in Humans?

Pirone JR[1], Akkina R[1], Garcia JV[1], Luciw P[2], Adamson L[2], Sykes C[1], White N[1], Schauer AP[1], Blake K[1], Burgunder E[1], Devanathan AS[1], Srinivas N[1], Rosen E[1], Kashuba ADM[1]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of California Davis, Davis, CA, USA

Poster No. 0475

Background

- For HIV cure strategies like “kick and kill” to succeed, antiretroviral (ARV) drugs must reach protective concentrations in putative viral reservoirs, including lymphoid tissue and sequestered sites like the brain and the genital tract.
- Inadequate ARV penetration into tissues may create pharmacologic sanctuaries where HIV is never fully eradicated, and from which HIV recrudescence can occur.[1]
- Extrapolating outcomes of animal studies to humans requires an understandng of ARV tissue distribution.
- Here, we characterize the penetration of 6 ARVs in 2 humanized mouse models, nonhuman primates (NHPs), and HIV+ humans.

Methods

Mice[2]

- 21 hu-HSC-Rag (RAGHu) and 18 bone marrow-liver-thymus (BLT) humanized mice were infected with $HIV_{Bal\ D7}$ for 10 and HIV_{JRcsf} for 6 days, respectively.
- All RAGHu mice were dosed with one of several ARV regimens for 10 days: EFV 10mg/kg (n=6) alone; atazanavir (ATZ) 140mg/kg (n=6) alone; or tenofovir (TFV) 208mg/kg, emtricitabine (FTC) 240mg/kg, raltegravir (RAL) 56mg/kg, maraviroc (MVC) 62mg/kg (n=6) in combination. All BLT mice received a combination of TFV, FTC, RAL, ATZ, and MVC at equivalent doses as above for 6 days.
- 20 RAGHu and 6 BLT mice were not infected.
- Mice were euthanized; plasma and tissues were collected at necropsy.

Non-Human Primates (NHPs)[2]

- Ten NHPs (6 male, 4 female) were infected with RT-SHIV for 4 weeks. Eight NHPs (6 male, 2 female) were not infected.
- All NHPs were dosed to steady-state with the following 6 ARVs: FTC 16 mg/kg, TFV 30 mg/kg, EFV 200 mg/day, RAL 200 mg/day, MVC 300 mg/day, and ATZ 540 mg/day.
- NHPs were euthanized; plasma and tissues were collected at necropsy.

Humans

- 17 human subjects’ (15 male, 2 female) tissues were obtained from National NeuroAIDS Tissue Consortium harvested 8-47 hours post dose.
- Female genital tract and colorectal concentrations obtained from data from U01AI095031.
- Quantified ARVs were: FTC, TFV, EFV, RAL, MVC, and ATZ.

ARV, Active Metabolite, and Endogenous Nucleotide Concentrations in Tissues

- ARV, emtricitabine triphosphate (FTCtp), tenofovir diphosphate (TFVdp), and endogenous nucleotide (dCTP, dATP) concentrations were measured in homogenized tissue by LC-MS/MS. Concentrations were converted from ng/ml to ng/g using a tissue density of 1.06 g/ml (Lower limit of quantitation, LLOQ: 0.002-0.01 ng/ml (ARVs), 0.22 ng/ml (metabolites)).

Statistical Analysis

- A Bayesian linear regression measurement-error model was used to characterize plasma and tissue concentration relationships.
- Metabolite to endogenous nucleotide ratios analyzed via Wilcoxon rank sum test with the Benjamini Hochberg P-value adjustment procedure.

Results

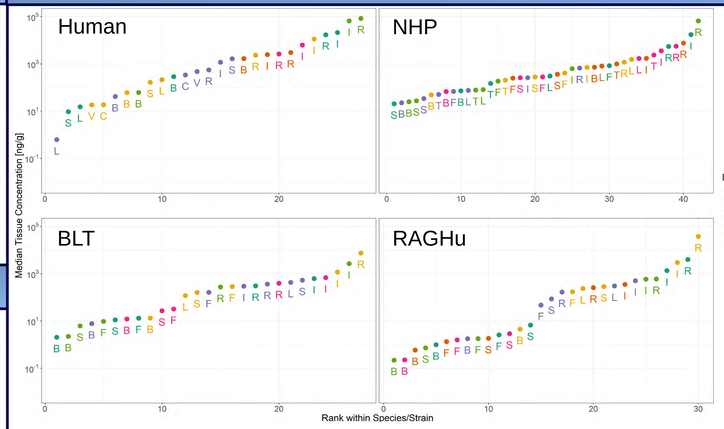


Figure 1. Rank plot of median tissue concentrations. For all species, ARV concentrations were highest in the gastrointestinal tract. (B) Brain, (F) Female genital tract, (I) Ileum, (L) Lymph Node, (R) Rectum, (S) Spleen, (T) Testes.

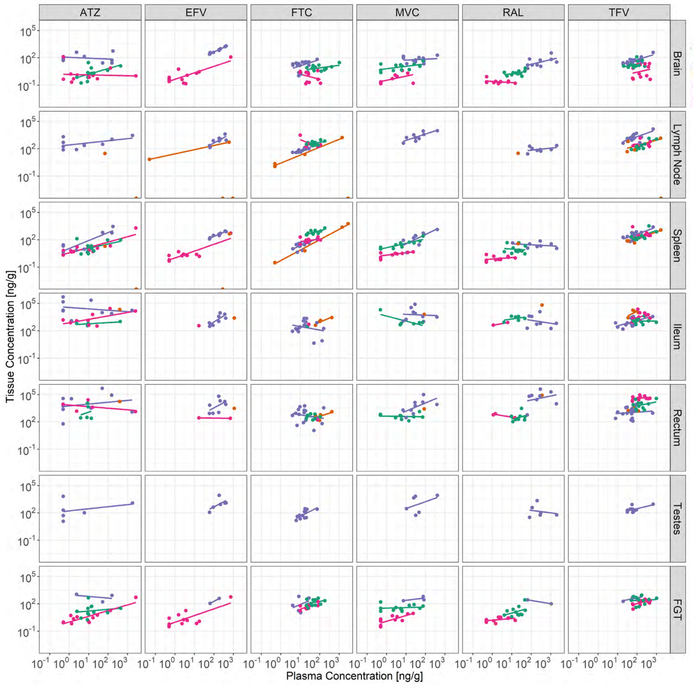


Figure 2. Correlation plots of tissue vs. plasma concentrations across all tissues for the 6 ARVs. Increasing NRTI doses would lead to increase tissue penetration in lymph nodes and spleen. FGT = Female genital tract.

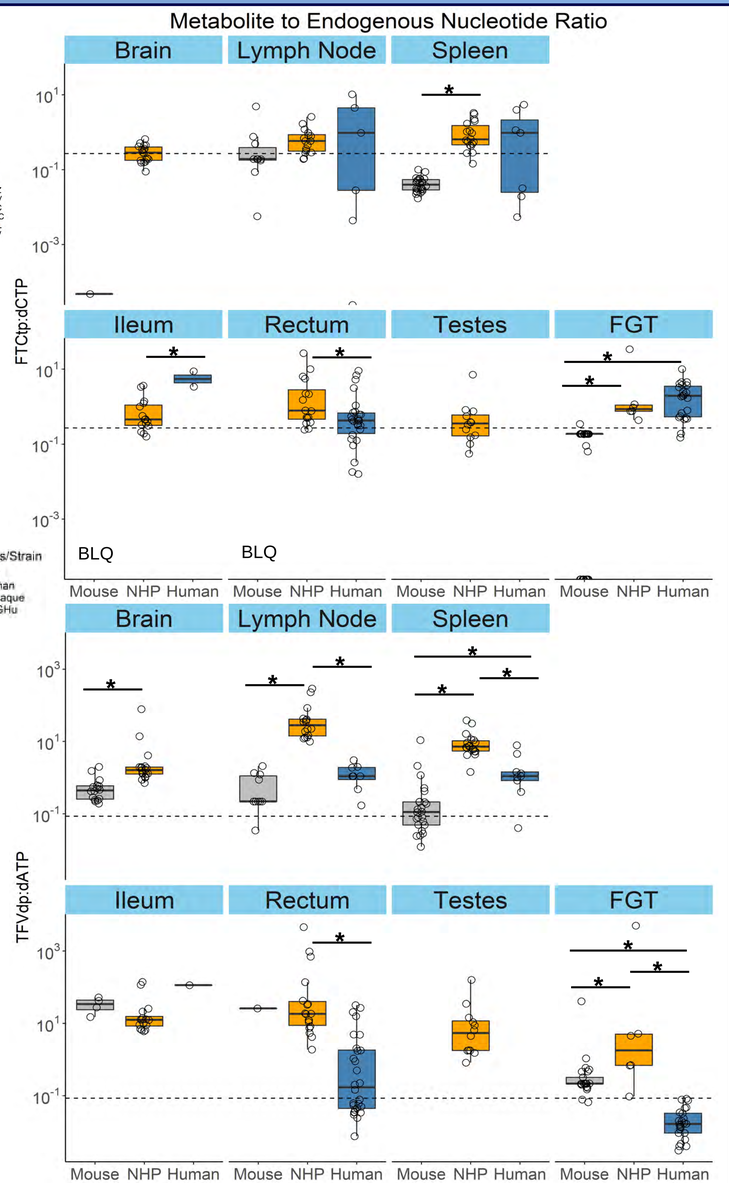


Figure 3. Metabolite to endogenous nucleotide ratio plots across nine tissues. Lines represent literature-derived IC_{90} values.[3] NHP ratios closely resembled those of humans. * = P-value < 0.05. BLQ = below limit of quantification. FGT = Female genital tract.

Conclusions

- NHP dosing strategies most closely mimicked tissue concentrations in humans.
  - Metabolite to endogenous nucleotide ratios for NHPs were similar to, or higher than, humans.
  - While humanized mice had lower plasma and tissue exposure, in general, tissue to plasma ratios were similar to NHPs and humans, suggesting similar tissue penetration processes.
- Correlation plots suggest:
  - For TFV and EFV, increasing doses would increase concentrations in all tissues for all species.
  - For TFV and FTC, increasing doses would increase secondary lymphoid organ (i.e. lymph nodes and spleen) concentrations in NHPs and humans.
- These results have implications on interpreting HIV treatment, prevention, or cure interventions between models.
  - Current ARV doses in NHPs mimic human tissue exposure.
  - NRTI active metabolite ratios in mice are lower than in NHPs or humans.
  - NRTI active metabolite ratios in NHPs are greater than or equal to those of humans.

References

1. Fletcher, CV. et al. Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues. *Proc Natl Acad Sci USA.* 2014;111:2307-2312.
2. Thompson CG et al. Multimodal analysis of drug transporter expression in gastrointestinal tissue. *AIDS.* 2017;31:1669-1678.
3. Cottrell ML et al. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. *J Infect Dis.* 2016;214:55-64.

Acknowledgements

We acknowledge the following funding sources:

- NIH R01AI111891
- University of North Carolina at Chapel Hill Center for AIDS Research P30AI50410
- NIH U01AI095031
- California National Primate Research Center P51OD011107
- Manhattan HIV Brain Bank U24MH100931
- Texas NeuroAIDS Research Center U24MH100930
- National Neurological AIDS Bank U24MH100929
- California NeuroAIDS Tissue Network U24MH100928