MK-8591 Concentrations at Sites of HIV Transmission and Replication

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Abstract

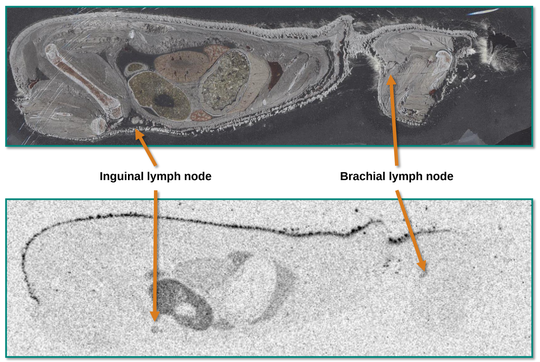
Background: MK-8591 is a long-acting nucleoside reverse transcriptase translocation inhibitor (NRTTI) that has demonstrated potent antiviral activity in HIV-1–infected subjects administered a once-weekly (QW) 10-mg dose as monotherapy in a clinical trial and in SIV-infected rhesus macaque models. MK-8591 extended-duration dosing potential was suggested by the long intracellular half-life of MK-8591-triphosphate (MK-8591-TP) in peripheral blood mononuclear cells (PBMCs) in vitro and in preclinical models. Here we describe the tissue distribution of MK-8591 and its anabolites in rats by quantitative whole-body autoradiography and in rhesus vaginal and rectal mucosa by biopsy.

Methods: Wistar Hannover rats dosed orally at 50 mpk (mg/kg) of [^{14}C]MK-8591 were sacrificed at 0.5 hours and 24 hours, cryosectioned (40 µm thick sagittal), and phosphor imaged after a 4 day exposure. Radioactivity in tissues was quantified using the blood standards along with Raytest AIDA image analysis software. For rectal and vaginal tissue distribution studies, monkeys were dosed 3.9 mpk orally on Days 1 and 8. PBMCs were isolated from blood collected at Days 1, 7, 14, and 21. Colorectal and vaginal biopsies were collected on Days 7 (predose) and 14, pooled separately, and snap-frozen with liquid nitrogen. PBMC and biopsy samples were analyzed by LC-MS/MS.

Results: In rat, MK-8591-related material distributed widely within 30 minutes of dosing and was notably enriched in lymphoid tissue (75.9 nmol-eq/g) compared with blood (lymph node:blood ratio = 2.7). In rat, MK-8591-related material remained enriched in lymphoid tissue at 24 hours (11.1 nmol-eq/g; lymph node:blood ratio = 7.1). In rhesus macaques, on Days 7 and 14, levels of MK-8591-TP in rectal tissue (36 pmol/g and 31 pmol/g) were similar to those measured in vaginal tissue (49 pmol/g and 78 pmol/g).

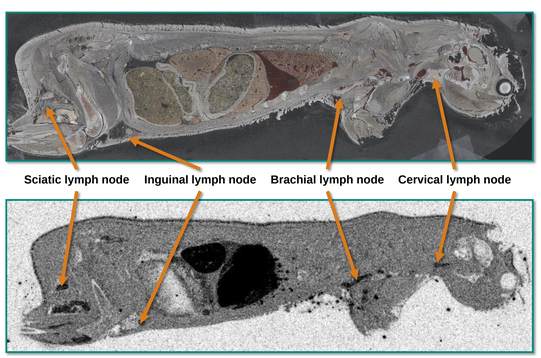
Conclusions: The levels of MK-8591-TP achieved in both rectal and vaginal tissue are comparable to the levels of tenofovir diphosphate observed in rectal tissue from human subjects treated with tenofovir disoproxil fumarate. Given the significantly greater potency of MK-8591 (IC_{50} = 0.2 nM) compared with TDF (IC_{50} = 73 nM), these data suggest utility of MK-8591 for prophylaxis in both men and women. In addition, as lymphoid tissues are sites of active HIV replication and persistence, the observation that MK-8591 is enriched in lymphoid tissues in rats suggests the potential to address the ongoing replication of HIV in lymph nodes.

QWBA Study [^{14}C]MK-8591 in Male Rats at 24 Hours After 50 mg/kg P.O. Single Dose



Top: Scanned optical image of 40 µm male rat whole-body sagittal sections. **Bottom:** Autoradiograph of 40 µm male rat whole-body sagittal sections. Dark areas represent presence of radiolabel-related material.

QWBA Study [^{14}C]MK-8591 in Male Rats at 0.5 Hours After 50 mg/kg P.O. Single Dose



Top: Scanned optical image of 40 µm male rat whole-body sagittal sections. **Bottom:** Autoradiograph of 40 µm male rat whole-body sagittal sections. Dark areas represent presence of radiolabel-related material.

MK-8591 Enriched in Lymphoid Tissue Compared With Blood

Lymph node:blood ratio

Lymph Nodes	0.5 hr	24 hr
Lymph node – brachial	2.69	7.80
Lymph node – inguinal	2.63	8.18
Lymph node – sciatic	3.06	ND
Lymph node – submandibular	2.47	5.39

MK-8591–associated radioactivity in lymph nodes exceeds blood levels at 0.5 and 24 hours post-dose

[^{14}C]MK-8591 concentrations in captured lymph nodes

	nmol-eq/g	
Lymph Nodes	**0.5 hr**	**24 hr**
Lymph node – brachial	75.17	12.12
Lymph node – inguinal	73.58	12.71
Lymph node – sciatic	85.63	ND
Lymph node – submandibular	69.04	8.37
LOQ	2.10	1.86

From 28-day rat tolerability study

Total intracellular DRM = ~16 µM at t = 2 hours post-dose on Day 28 of 50 mg/kg/day group

- May be more appropriate to use LN/PBMC ratios to assess potential accumulation in LN

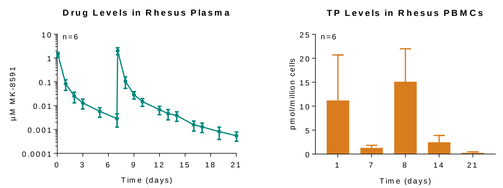
MK-8591 QW PK Study Design

Day 1 → Day 7 → Day 14 → Day 21

Dose MK-8591 3.9 mpk QW PO; QW dosing at Day 1 and Day 7

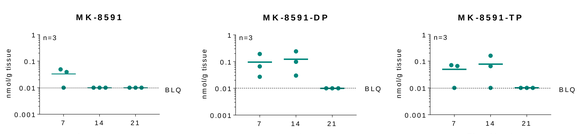
- 3 male + 3 female Rhesus monkeys per drug
- Sample collection for 3 weeks
- Mucosal tissue and secretions at Days 7, 14, and 21
- PBMC samples at Days 1, 7, 8, 14, and 21
- Plasma PK samples collected almost daily

Plasma PK and TP Level in PBMCs

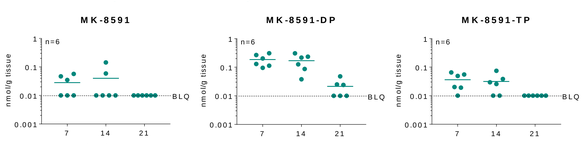


The Level of MK-8591 Anabolites in Monkey Rectal and Vaginal Tissues at 3.9 mpk Dosed at Day 1 and Day 7

A. Vaginal tissue



B. Rectal tissue (3 male and 3 female)



The Level of MK-8591 Anabolites in Monkey Rectal and Vaginal Tissues at 3.9 mpk Dosed at Day 1 and Day 7

	MK-8591 (nmol/g)			MK-8591-DP (nmol/g)			MK-8591-TP (nmol/g)		
Days	7	14	21	7	14	21	7	14	21
Vaginal	0.033	BLQ	BLQ	0.095	0.123	BLQ	0.049	0.078	BLQ
Rectal	0.028	0.041	BLQ	0.186	0.168	0.021	0.036	0.031	BLQ

Assuming nmol/g = nmol/mL, the concentration of the anabolites are as follows:

	MK-8591 (nM)			MK-8591-DP (nM)			MK-8591-TP (nM)		
Days	7	14	21	7	14	21	7	14	21
Vaginal	33	BLQ	BLQ	95	123	BLQ	49	78	BLQ
Rectal	28	41	BLQ	186	168	21	36	31	BLQ

- As opposed to TDF (the TFV-DP level is much lower in vaginal tissues), the level of anabolites in vaginal and rectal tissues are comparable for MK-8591
- The level of TP at 3.9 mpk is comparable to the level of TFV-DP in rectal tissue at a dose of 300 mg in humans. Of note, uptake of MK-8591 is more efficient in humans than in monkeys
- The intrinsic EC_{50} of MK-8591-TP (30 nM) is 10 times more potent than TFV-DP (340 nM) in the antiviral assay with PBMCs

Conclusions

- The levels of MK-8591-TP achieved in both rectal and vaginal tissue are comparable to the levels of tenofovir diphosphate observed in rectal tissue from human subjects treated with tenofovir disoproxil fumarate
- Given the significantly greater potency of MK-8591 (IC_{50} = 0.2 nM) compared with TDF (IC_{50} = 73 nM), these data suggest utility of MK-8591 for prophylaxis in both men and women
- As lymphoid tissues are sites of active HIV replication and persistence, the observation that MK-8591 is enriched in lymphoid tissues in rats suggests the potential to address the ongoing replication of HIV in lymph nodes

Reference:

Kashuba, ADM., 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. June 8-10, 2016, Washington, DC, USA.