

EFdA OFFERS COMPLETE PROTECTION FROM REPEATED PENILE HIV CHALLENGES

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BACKGROUND:

Unprotected heterosexual intercourse is the most common route of HIV transmission. Men comprise approximately half of the HIV-infected population worldwide. Sexually transmitted HIV infections in exclusively heterosexual men are acquired through the penis. Prevention methods for this mode of transmission are condom use and circumcision. However, low adherence to condom use and the fact that 40% of circumcised men are not protected highlight the need for additional more effective prevention strategies. We tested 4'-ethynyl-2'-fluoro-2'-deoxyadenosine (EFdA), a potent NRTTI with low cytotoxicity, for the prevention of penile HIV transmission.

METHODS:

- Male genital tract (MGT) of bone marrow/liver/thymus (BLT) humanized mice was evaluated for human cell reconstitution by flow cytometry.
- Location of human cells in the MGT was assessed by immunohistochemistry and compared to human tissue.
- HIV infected BLT mice were treated with EFdA orally (1.8 mg/kg) and suppression of the HIV infection in MGT tissues evaluated to confirm EFdA penetration.
- BLT mice treated with EFdA (n=9) or untreated (n=11) were exposed to multiple doses of transmitted/founder HIV_{CH040} via the penis.
- Animals were evaluated for HIV infection for four weeks after last HIV exposure (DNA and RNA)

EFdA efficiently penetrate to the male genital tract and protects from penile HIV transmission.

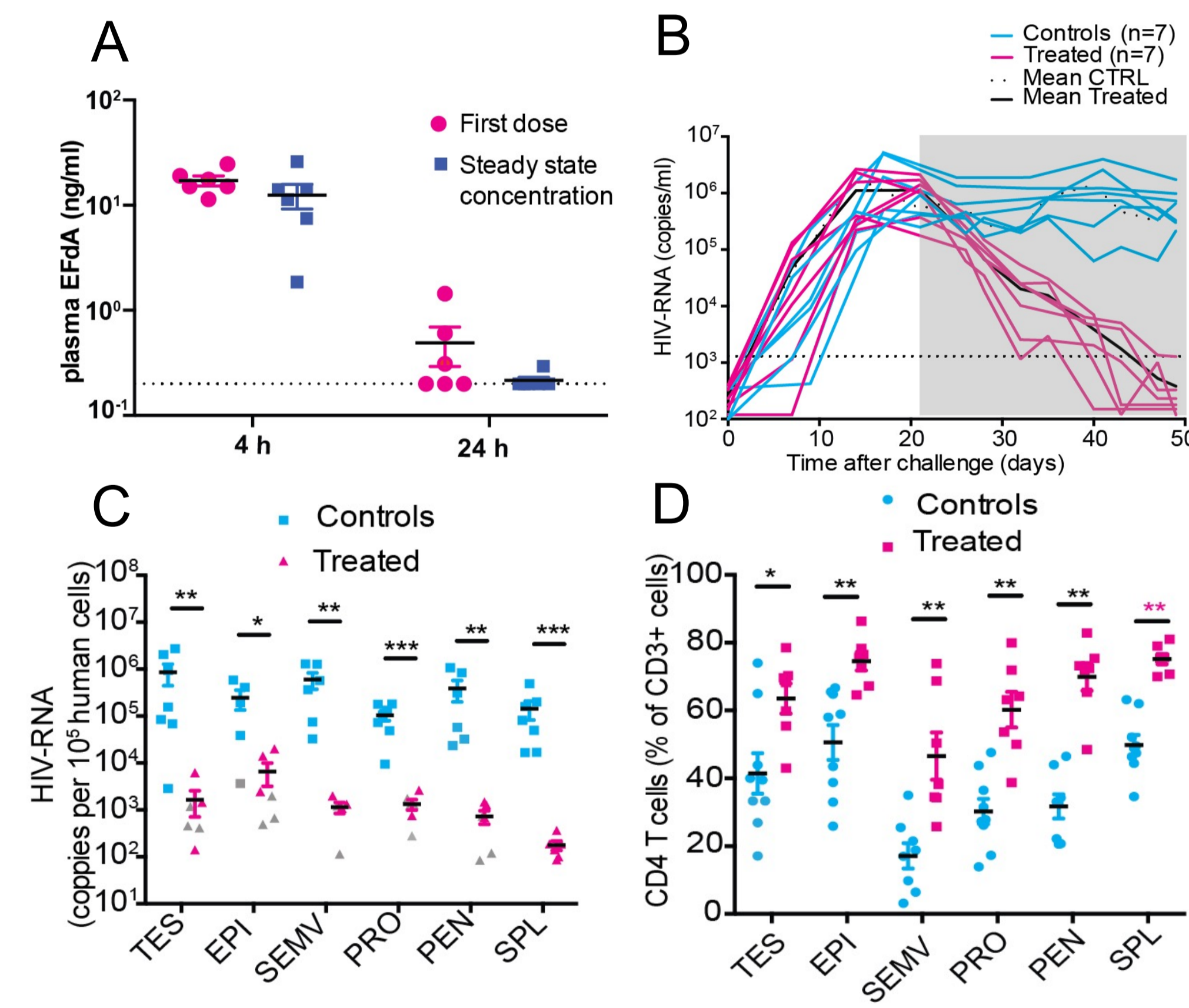
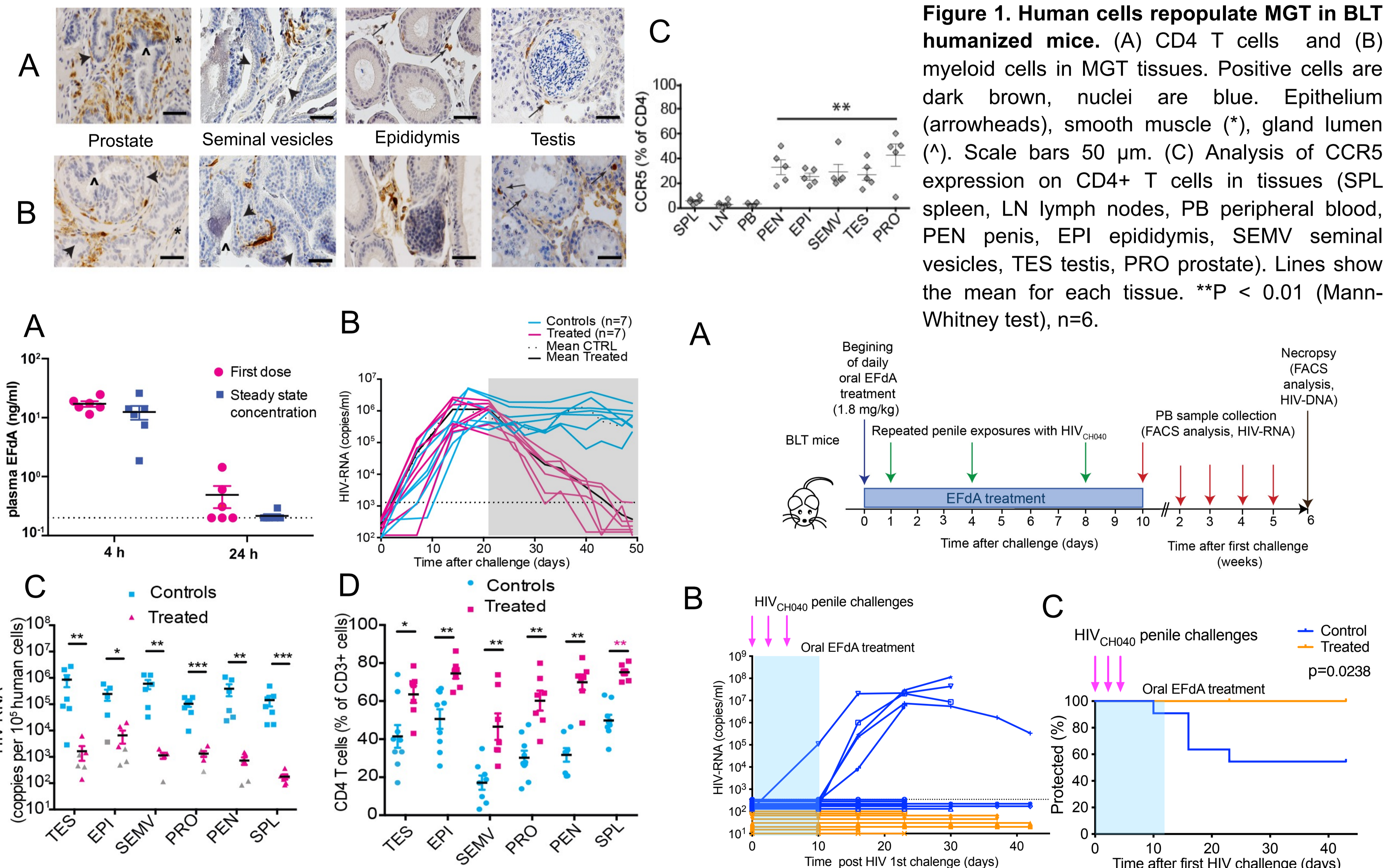


Figure 2. EFdA effectively reduces HIV in peripheral blood and throughout the tissues of the MGT. HIV_{JR-CSF} infected mice were treated with daily oral EFdA (1.8 mg/ml) and monitored for HIV-RNA in peripheral blood (A) EFdA concentration in peripheral blood after first and 7th daily dose 1.8mg/kg. (B) HIV-RNA in plasma of individual mice. The grey area indicates the EFdA treatment, n=7 per group, dotted lines indicate limits of detection. Cell-associated HIV-RNA (D), and CD4⁺ T cell levels (E) in tissues four weeks after initiation of EFdA treatment TES testis, EPI epididymis, SEMV seminal vesicles, PRO prostate, PEN penis, SPL spleen. Grey symbols indicate samples below limit of detection, black lines are mean values for each data set. (*P < 0.05, **P < 0.01, ***P < 0.001, Mann-Whitney test)

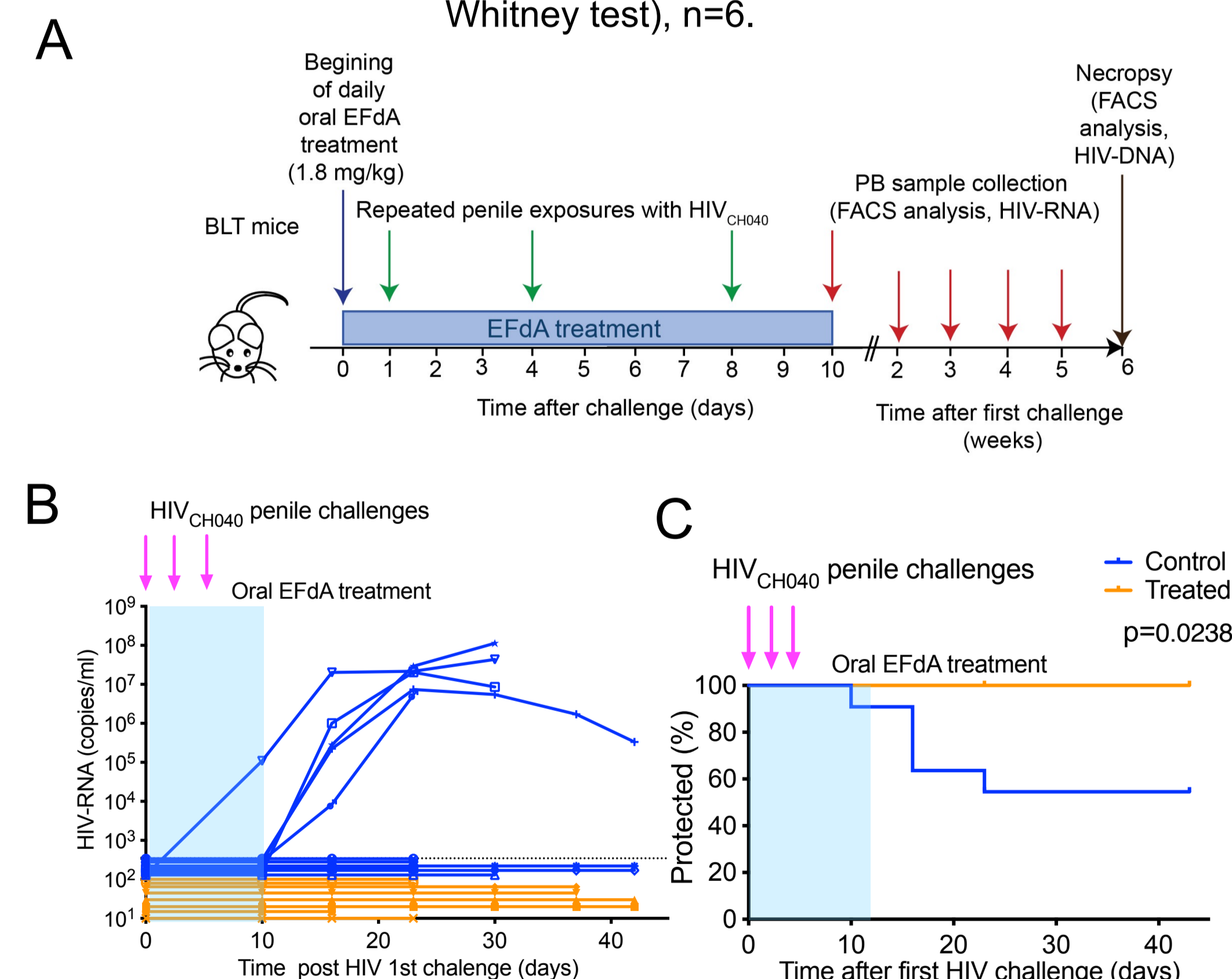


Figure 3. EFdA protects from penile HIV transmission. (A) Experimental design. BLT humanized mice untreated (n=11) or treated daily with oral EFdA (n=6) were challenged with HIV_{CH040} (1.8 x 10⁶ TCID₅₀) penily at day 1, 4 and 8 of treatment. HIV-RNA in peripheral blood was monitored longitudinally. Four weeks after the last HIV challenge, multiple tissues were analyzed for cell-associated HIV-DNA (B) HIV-RNA in plasma of individual mice. (C) Kaplan-Meier graph showing significant protection from penile HIV transmission in of EFdA-treated BLT mice. The blue shaded area indicates the time of daily oral treatment with EFdA (1.8mg/kg). The dotted line in B indicates the HIV-RNA limit of detection (346 copies/ml).

RESULTS:

- MGT of BLT humanized mice including testes, epididymis, seminal vesicles, prostate, and urethra were repopulated with human T and myeloid cells and their location within tissues was comparable to human (Figure 1A, B).
- The majority of the human T cells in the MGT express CD4 and CCR5 and were susceptible to HIV after intravenous exposure to HIV (Figure 1C).
- Treatment of HIV infected BLT mice with EFdA results in a dramatic reduction (2-3 log) in HIV replication and the restoration of CD4⁺ T cell levels throughout the entire MGT, demonstrating the efficient penetration of EFdA into the entire MGT (Figure 2).
- Penile exposures to HIV_{CH040} resulted in systemic HIV infection in 6 of 11 humanize mice. None of the mice treated with EFdA became infected (Figure 3, p=0.0238).

CONCLUSIONS:

Our data demonstrate efficient suppression of HIV by EFdA in the entire MGT. Pre-exposure prophylaxis with EFdA efficiently prevents penile HIV transmission. These data support further clinical development of EFdA as a potential pre-exposure prophylaxis agent to prevent HIV transmission in men.