XV-122 Provides Ultra-Long Acting Dolutegravir Exposure in Rhesus Macaques

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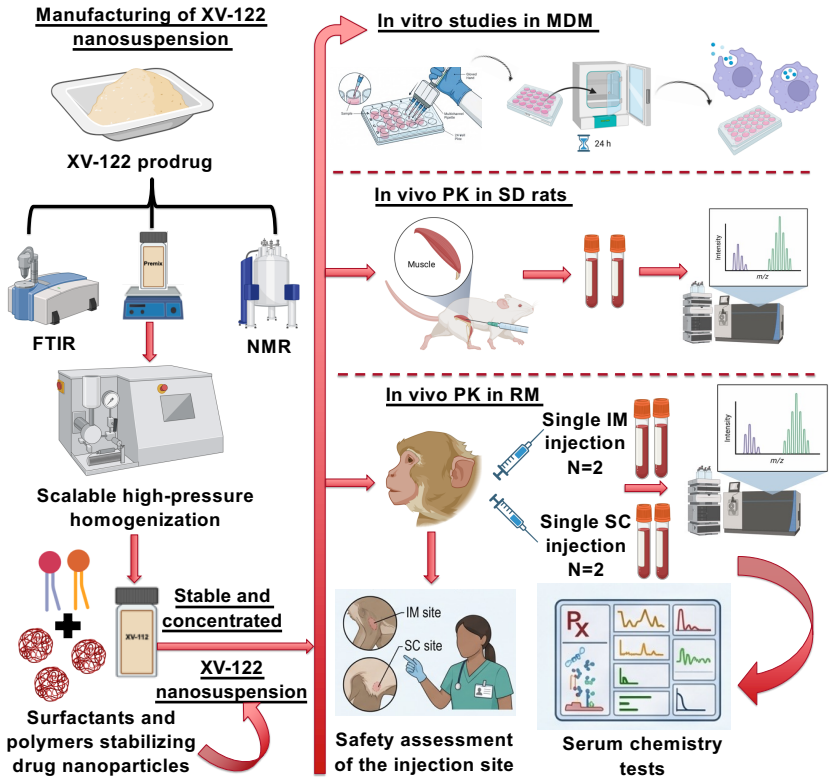
Background

Long-acting antiretroviral therapies have improved patient satisfaction and outcomes for HIV prevention and treatment. Ultra-long acting (ULA) ART represents the next step in HIV prevention and treatment, offering less frequent dosing and even greater convenience. A prodrug nanosuspension (XV-122) of a homodimeric dolutegravir (DTG) was developed to meet a next-generation, patient-centric need. DTG, an integrase strand transfer inhibitor, is widely used in first-line combination therapy, demonstrating both high potency and a high barrier to HIV drug resistance. In rodent pharmacokinetic (PK) studies, XV-122 maintained therapeutic DTG concentrations for up to four months after a single low-volume intramuscular (IM) or subcutaneous (SC) injection. The current study demonstrates ULA PK profile of a single IM or SC injection of XV-122 in rhesus macaques.

Methods



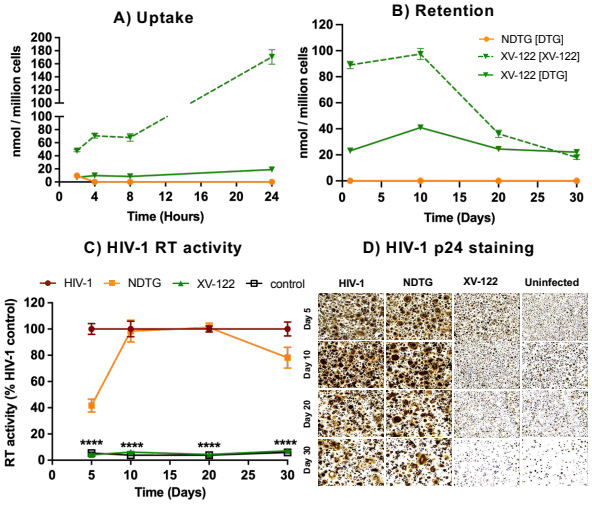


Fig. 2. Drug uptake and retention in human MDMs. **(A)** Uptake and **B)** Retention were measured with 50 µm of drug. Intracellular drug levels were quantified by UPLC-UV/Vis. Results were expressed as Mean ± SEM. **C)** HIV-1 RT activity of NDTG and XV-122–treated MDMs. ****P < 0.0001 XV-122 vs. NDTG. Uninfected cells without treatment served as negative controls. HIV-1-infected cells without treatment served as positive controls. Results were normalized to positive control cells. Results were analyzed by two–way ANOVA with Dunnett's multiple comparison tests. **D)** Antiretroviral responses were recorded after challenge with HIV-1 $_{ADA}$ at a multiplicity of infection (MOI) of 0.1 infectious virions/cells at recorded times following treatment with either NDTG or XV-122 at 50 µM concentrations for 8 h. Uninfected cells without treatment served as negative controls. HIV-1-infected cells without treatment served as positive controls. HIV-1 p24 antigen levels were assessed in fixed MDM by immunohistochemical staining.

Results

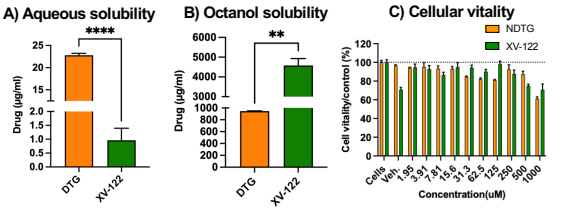


Fig. 1. Prodrug characterization. A) Aqueous and **B)** octanol solubility of DTG and XV-122 prodrug. Results are expressed as the mean ± SEM for n = 3. **C)** Cellular vitality was assessed in MDM by MTT assay after 24 h treatment with either NDTG or XV-122 nanosuspension over a range of concentrations (1.95 -1000 µM). Results are normalized to untreated control cells and are expressed as Mean ± SEM for n = 4

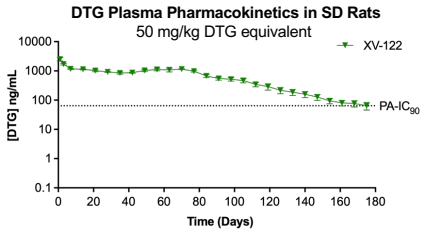


Fig. 3. Plasma DTG levels: SD rats were administered a single intramuscular injection of XV-122 at a dose of 50 mg DTG eq./kg on day 0, and plasma DTG levels were monitored over 180 days. Drug levels were quantified using LC-MS/MS, and data sets are expressed as Mean ± SEM. (n=5). Solid and dotted line represents 1x (64 ng/ml) the protein-adjusted 90% inhibitory concentration of DTG.

Parameters	XV-122
$T_{1/2}$ (Day)	38.15
T_{max} (Day)	1
C_{max} (ng/ml)	2517.8
AUC $_{0-\infty}$ (Day*ng/ml)	116913.3
MRT$_{0-\infty}$ (Day)	61.3

Table 1. PK parameters after a single IM injection of 50 mg/kg DTG eq. dose of XV-122. $T_{1/2}$ = apparent half life; C_{max}= Maximum plasma concentration of the drug; T_{max} = Time of maximum plasma concentration; AUC$_{0-\infty}$ = Area under curve from 0 hour to infinity; MRT$_{0-\infty}$ = Mean residence time from 0 hour to infinity. All values are expressed as mean, expect T_{max} is expressed as median (minimum- maximum).

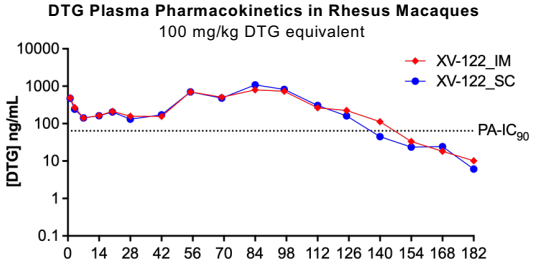


Fig. 4. Plasma concentration-time profiles of DTG following a single IM or SC dose of XV-122 in Rhesus macaques. Four male rhesus macaques were administered a single IM (N=2) or SC (N=2) of XV-122 at a dose of 100 mg. DTG-eq./kg. Drug levels were quantified by UPLC MS/MS. Results are expressed as mean ± SEM

Parameters	XV-122 (IM)	XV-122 (SC)
$T_{1/2}$ (Day)	17.401	13.973
T_{max} (Day)	69.5	84
C_{max} (ng/ml)	866.2	1083.45
AUC $_{0-\infty}$ (Day*ng/ml)	56623.4	59568.41
MRT$_{0-\infty}$ (Day)	77.204	76.75

Table 2. PK parameters after a single IM or SC injection of 100 mg/kg DTG eq. dose of XV-122. $T_{1/2}$ = apparent half life C_{max}= Maximum plasma concentration of the drug; T_{max} = Time of maximum plasma concentration; AUC$_{0-\infty}$ = Area under curve from 0 hour to infinity; MRT$_{0-\infty}$ = Mean residence time from 0 hour to infinity. All values are expressed as mean, expect T_{max} is expressed as median (minimum- maximum).

Conclusion

- XV-122 was safe and was efficiently taken up by the macrophages.
- XV-122 maintained therapeutic concentrations up to four months in rodents.
- XV-122 demonstrated a ULA PK profile of DTG over three months in RM after a single IM or SC injection.

Funding Sources

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