staying on current ART, switching to another oral ART or switching to a LAI ART. DCE treatment attributes include dosing frequency, side effects, forgivability, food/mealtime restrictions, and mode of administration. Pilot data for US patients is included here; the main survey will include approximately 550 patients and 450 physicians.

Results. Of 51 PLHIV completing the pilot survey, 80% were male, mean age was 54 years, and 63% were on ART for ≥10 years. Switching ART was common, with 55% reporting changing their ART ≥ 3 times. Just under half of patients (47%) were not totally satisfied with their current ART. Most common reasons for dissatisfaction included daily reminder of having HIV (31%) and having to take medicine every day (28%). Just over a quarter of patients (28%) reported forgetting to take their ART in the prior month. Across all DCE choices, patients preferred to remain on their current treatment 47% of the time, while 45% of the time patients preferred switching to the LAI, and for the remaining 8%, patients chose switching to another oral ART regimen.

Conclusion. Despite advances in ART, treatment challenges remain. Among the treatment-experienced PLHIV in this pilot survey, over half of their choices resulted in switching to an alternative regimen, and when opting to switch, most patients preferred the long-acting injectable treatment regimen.

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2500. Fostemsavir Drug–Drug Interaction Profile, an Attachment Inhibitor and Oral Prodrug of Temsavir, for Heavily Treatment Experienced HIV-1-Infected Patients

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Background. Fostemsavir (FTR) is a first-in-class attachment inhibitor being evaluated in heavily treatment-experienced (HTE) HIV-1-infected patients. Active temsavir (TMR) binds to viral envelope glycoprotein 120 and prevents viral attachment and entry into host CD4+ T cells. TMR is primarily metabolized by esterase-mediated hydrolysis with contributions from cytochrome P450 (CYP) 3A4. TMR does not inhibit/induce major CYP or uridine diphosphate glucuronosyltransferase (UGT) enzymes and is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate. TMR and/or its metabolites inhibit BCRP and organic anion transporter protein 1B1/3 (OATP1B1/3). FTR DDI profile informs coadministration with antiretrovirals (ARV) and other therapeutic classes.

Methods. DDI data from 13 studies were compiled to inform the impact of 17 drugs or drug combinations on TMR and the impact of TMR on 15 drugs such as ARVs, rifamycins, opioid substitutes, statins, oral contraceptives (OC), and H2-antagonsits.

Results. FTR with CYP3A4, P-gp, and/or BCRP inhibitors increase TMR concentrations; but, do not pose clinical concern at therapeutic dose. TMR may be administered with weak/moderate inducers with or without coadministration of CYP3A4, P-gp, and/or BCRP inhibitors such as RTV or COBI. Coadministration with strong inducers is contraindicated. FTR may be coadministered with RBT with or without a PK enhancer. However, co-administration of FTR with RIF is contraindicated. FTR can be given with drugs that increase gastric pH; famotidine did not impact TMR PK. TMR may increase concentrations of drugs that are substrates of OATP1B1/3 and BCRP; therefore, most statins require dose reduction (e.g., rosuvastatin dose is limited to ≤10 mg QD). TMR increased EE exposure 40% with no impact on NE; therefore, FTR may be coadministered with OCs containing ≤30 µg EE. TMR had no clinically meaningful impact on TDF, DRV/RTV, ATV/RTV, ATV, RTV, ETR, MET, or BUP/norBUP PK (Table 1).

Conclusion. FTR can be coadministered with ARVs and most common treatments used to manage HIV co-infections or comorbidities without dose adjustment of either drug except for select HMG-CoA reductase inhibitors and EE-containing OCs. Strong CYP3A inducers are contraindicated.

Table 1. FTR drug-drug interaction profile, an attachment inhibitor and oral prodrug of TMR, for heavily treatment experienced HIV-1 infected patients (data presented at geometric mean ratio, GMR).

Concomitant Drug Name	Impact on TMR GMR	Impact on Concomitant Drug GMR	
Maraviroc (MVC)	TMR ↔ Cmax ↑ 13%, AUC ↑ 10% Ct ↓ 10%	MVC ↔ Cmax ↑ 1%, AUC ↑ 25% Ct ↑ 37%	
Raltegravir (RAL)	TMR ↔*	RAL ↔*	
Etravirine (ETR)	TMR ↓ Cmax ↓ 46% AUC ↓ 50% Ct ↓ 52%	ETR ↔ Cmax ↑ 11% AUC ↑ 11% Ct ↑14%	
Tenofovir (TDF)	TMR ↔ Cmax ↓ 1% AUC ↔ 0% Ct ↑ 13%	TDF ↑ Cmax ↑ 18% AUC ↑ 19% Ct ↑ 28%	
Cobicistat (COBI)	TMR ↑ Cmax ↑ 71%, AUC ↑ 93% Ct ↑ 136%	ND	
Ritonavir (RTV)	TMR ↑ Cmax ↑ 50%, AUC ↑ 45% Ct ↑ 44%	RTV ↔ Cmax ↑ 14% AUC ↑ 9% Ct ↑ 7%	
Atazanavir (ATV)/ritonavir (RTV)	TMR ↑ Cmax ↑ 66%, AUC ↑ 54% Ct ↑ 57%	ATV ↔ Cmax ↑ 3% AUC ↑ 9% Ct ↑ 19%	RTV ↔ Cmax ↑ 2% AUC ↑ 7% Ct ↑ 22%
Darunavir (DRV)/COBI	TMR ↑ Cmax ↑ 76%, AUC ↑ 97% Ct ↑ 134%	ND	
Darunavir (DRV)/RTV	TMR ↑ Cmax ↑ 52%, AUC ↑ 63% Ct ↑ 86%	DRV ↔ Cmax ↓ 2% AUC ↓ 6% Ct ↓ 5%	RTV ↔ Cmax ↔ 0%, AUC ↑ 15% Ct ↑ 19%
Darunavir (DRV)/RTV + ETR	TMR ↑ Cmax ↑ 55%, AUC ↑ 34% Ct ↑ 33%	DRV ↓ Cmax ↓ 9% AUC ↓ 6% Ct ↓ 12%	RTV ↑ Cmax ↑ 14% AUC ↑ 9% Ct ↑ 7%	ETR ↔ Cmax ↑ 18% AUC ↑ 28% Ct ↑ 28%
Buprenorphine (BUP), Norbuprenorphine (norBUP), Methadone (R-/S-MET)	ND	BUP ↔ AUC ↑ 30% Cmax ↑ 24%	norBUP ↔ AUC ↑ 39% Cmax ↑ 24%	R-MET ↔ AUC↑ 13% Cmax ↑ 15%	S-MET ↔ AUC ↑ 15% Cmax ↑ 15%
Famotidine	TMR ↔ Cmax ↑ 1%, AUC ↑ 4% Ct ↓ 10%	ND	
Ethinyl estradiol (EE)	ND	EE ↑ AUC ↑ 39% Cmax ↑ 40%	
Norethindrone acetate (NE)	ND	NE ↔ AUC ↑ 8% Cmax ↑ 8%	
Rifabutin (RBT)	TMR ↓ Cmax ↓ 27%, AUC ↓ 30% Ct ↓ 41%	ND	
Rifabutin (RBT) + RTV	TMR ↑ Cmax ↑ 50%, AUC ↑ 66% Ct ↑ 118%	ND	
Rifampicin (RIF)	TMR ↓ Cmax ↓ 76%, AUC ↓ 82%	ND	
Rosuvastatin	ND	Rosuvastatin ↑ Cmax ↑ 78% AUC ↑ 69%	

*compared to historical data

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2501. CCR5 Targeted ARV Loaded Nanoparticle: Dual Protection for HIV Functional Cure

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Background. One of the NIH high-priority HIV/AIDS research objectives is to discover novel therapeutics aimed at developing safe, tolerable, strategies that targets cellular protein to induce long-term antiviral suppression. This current research aims at designing a novel targeted nano-formulation combining cell targeting and antiretroviral therapy to provide double protection against HIV-1.

Methods. CCR5 targeted combination antiretroviral drugs (cARV) loaded nanoparticles (NPs) were synthesized based on water-in-oil-in-water (W-O-W) emulsion methodology. For targeting CCR5+ T cells, a modified high affinity CCR5 monoclonal Ab (XFCCR5 mAb), was isolated from XF-CCR5 hybridoma cells. The XFCCR5 mAbs were covalently conjugated through their C-terminus by replacing the NHS group on FTC+DTG NPs with covalent amide bond. The CCR5 mAb binding was evaluated by SDS–PAGE methods. The CCR5-specific binding affinity of XFCCR5-FTC+DTG NP in compared with XFCCR5 monoclonal antibody (mAb) was evaluated by flow cytometry using CD4+CCR5+ TZM-bl cell line and PBMCs. The intracellular pharmacokinetic (PK) profile in TZMbl cells was evaluated by LC-MS/MS analysis, whereas *in vitro* efficacy was evaluated based on Steady-Glo® Luciferase Assay System using TZM-bl cells.

Results. XFCCR5-FTC+DTG NPs obtained averaged 173 ± 23 nm (mean ± SEM, n = 3) with 2.2 ± 0.47 mg XFCCR5 mAb bound per mg cARV NP. The formulation % entrapment efficiency of DTG and FTC respectively, to be 55 ± 1.6% and 42.6 ± 5.6%. The specific binding affinity (K_m) of XFCCR5-FTC+DTG NP and XFCCR5 mAb were estimated to be 0.0057 and 0.0377, higher compared with wild-type anti-CCR5 mAb with higher K_m value 0.303. Finally, the 4-day HIV-infection protection study result illustrates IC_{50} in case of XFCCR5-FTC+DTG NP and XFCCR5 NP to be as low as 0.0069 and 0.0031 µg/mL, respectively, compared with 1.771 µg/mL for XFCCR5 mAb (Figure 1, TZM-bl and Figure 2, PBMCs).

Conclusion. This nano-formulation aimed at duel protection by preventing HIV binding to CCR5+CD4+T cell due to CCR5 receptor blocking. These result support protection against HIV and maintenance of cARV drug levels. This novel formulation could be supportive of immune-alternative to achieve functional-cure against HIV.

Figure 1. Comparative binding affinity study in TZM-bl cells

Michaelis-Menten Best-fit values	anti-CCR5 mAb	XFCCR5 mAb	XFCCR5-FTC+DTG NP
Vmax	109.4	98.09	99.69
Km	0.3035	0.03768	0.005701

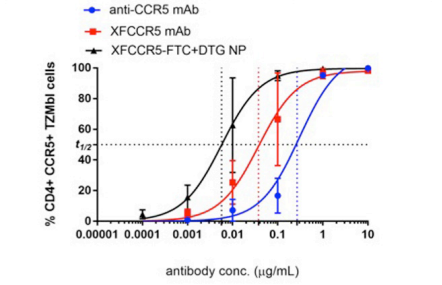
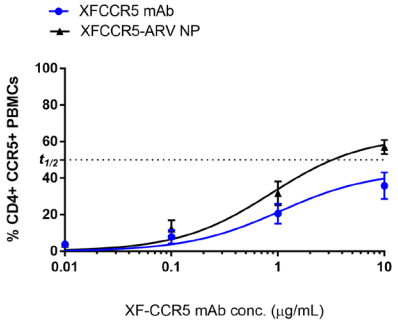


Figure 2. Binding affinity of CCR5 antibody in PBMCs

Michaelis-Menten Best-fit values	XFCCR5 mAb	XFCCR5-ARV NP
Vmax	43.91	63.3
Km	1.051	0.8634



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