# Comparison of Combination ART Regimens for Viral Suppression in SIV-Infected Rhesus Macaques

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## ABSTRACT

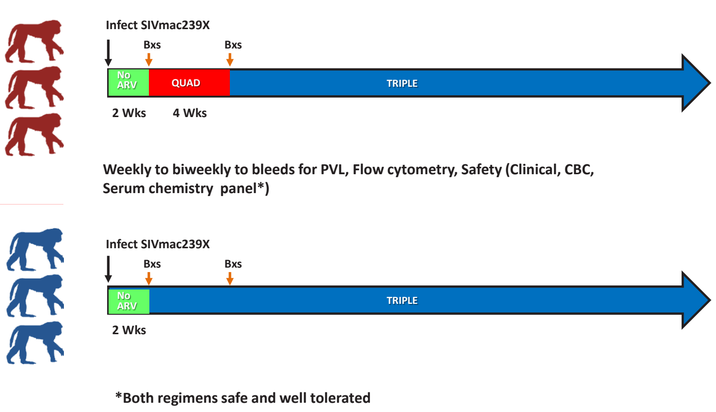
**Background: Nonhuman primate (NHP) models of human HIV infection, including the most commonly used model involving SIV-infected Indian rhesus macaques, represent an important component of the HIV cure research agenda. Feasible, sustainable combination antiretroviral treatment (cART) regimens to achieve clinically relevant levels of suppression (SIV plasma RNA < 30 copies/ml) are an essential element to enable use of such models in evaluation of experimental HIV cure strategies, but developing such regimens has proven challenging.**

**Methodology: We compared two different cART regimens (Tenofovir disoproxyl fumarate/Emtricitabine/Dolutegravir; TDF/FTC/DTG vs. Tenofovir disoproxyl fumarate/Emtricitabine/Dolutegravir/Darunavir; TDF/FTC/DTG/DRV), both given as a single, daily, co-formulated subcutaneous injection, in SIVmac239 infected Indian rhesus macaques (n = 3 each), with treatment initiated 2 weeks after intravenous infection. After the initial 4 weeks of treatment, all animals received the TDF/FTC/DTG regimen. We evaluated drug levels, plasma viremia, cell associated SIV RNA and DNA and immune activation.**

**Results: Both regimens were well tolerated based on clinical and laboratory (CBC and serum chemistry panel) evaluations. Starting from pretreatment plasma viral loads of ~3-4 X $10^7$ SIV RNA copies/ml, both regimens provided comparable 4 log declines in plasma viremia over the first 4 weeks of treatment, associated with decreased evidence of SIV infection related immune activation, based on HLA-DR and Ki67 expression. Continued treatment of all animals with TDF/FTC/DTG after the initial 4 weeks of cART produced continued declines in plasma viremia, to < 30 copies/ml in all animals, by 22 weeks post-infection (20 weeks on cART).**

**Conclusions: Both regimens resulted in prompt, effective suppression of SIVmac239 replication, as reflected by plasma viremia. There was no clear advantage associated with the addition of Darunavir to the regimen during the initial four weeks of treatment, and with continued treatment with TDF/FTC/DTG all animals were suppressed to < 30 copies/ml. TDF/FTC/DTG is an effective suppressive regimen in SIV-infected Indian rhesus macaques, and should facilitate NHP model studies of interventions targeting residual virus in cART suppressed individuals. TDF/FTC/DTG activity was comparable to that of the same regimen using Tenofovir (TFV) instead of TDF evaluated in prior studies; use of TDF instead of TFV in the combination should help minimize potential renal toxicities with long term administration.**

## EXPERIMENTAL DESIGN




## cART Formulations for Daily SubQ Administration

**TDF-based Triple TDF/FTC/DTG (5.1/50/2.5 mg/kg s.c. q.d.)**

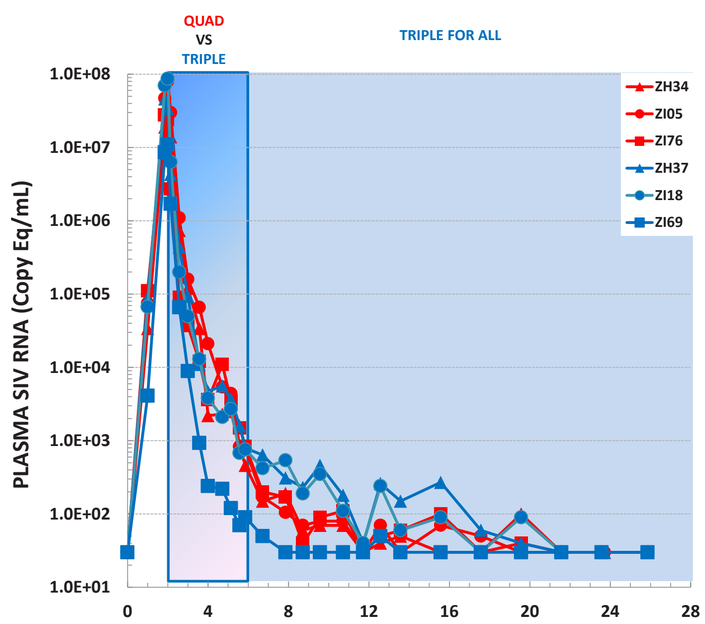
**TDF-based Quad TDF/FTC/DTG/DRV (5.1/50/2.5/40 mg/kg s.c. q.d.)**

**TFV-based Triple TFV/FTC/DTG (20/50/2.5 mg/kg s.c. q.d.)**
*(separate study)*

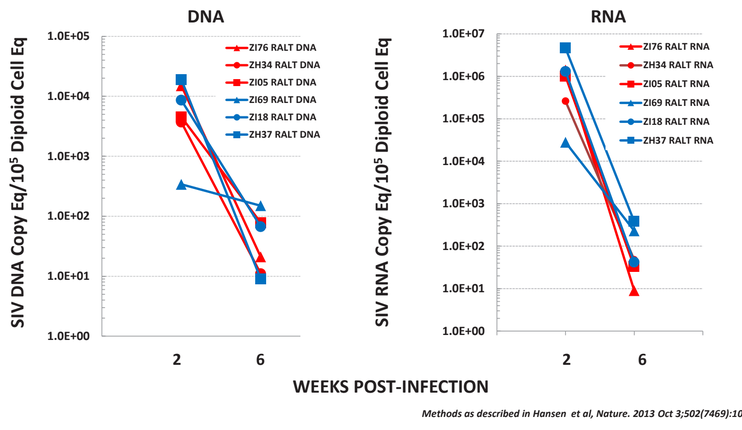
## TFV, DTG and DRV Plasma Drug Levels after s.c. Administration in Healthy and SIV+ Rhesus Macaques

| | Target | TDF-Triple SIV | Multiple of Target | TDF-Quad SIV | Multiple of Target | TFV-Triple Healthy | Multiple of Target |
|---|---|---|---|---|---|---|---|
| TFV $C_{2hr}$ (nM) | < 36,000* | 1786 | 0.05 | 1622 | 0.045 | 2130 | 0.06 |
| TFV $C_{SS}$ (nM) | 53* | 204 | 3.8 | 196 | 3.7 | 59 | 1.1 |
| DTG $C_{SS}$ (nM) | 509** | 3295 | 6.5 | 1986 | 4 | 1121 | 2.2 |
| DRV $C_{SS}$ (nM) | 268*** | NA | NA | 3956 | 14.8 | 467 | 1.7 |

Mean plasma values of n=3 animals per study and per time point
*based on TFV 20mg/kg/day s.c.
**Target DTG Cmin=509nM (SIV $PAEC_{95}$)
***Target DRV Cmin=268nM (SIV $PAEC_{95}$)




## CELL ASSOCIATED SIV VIRAL LOAD: RECTAL BIOPSIES




*Methods as described in Hansen et al, Nature. 2013 Oct 3;502(7469):100-4.*

## CONCLUSIONS

**Both TDF-based triple and quad ARV formulations were safe and well tolerated over the duration studied**

**Both TDF-based triple and quad ARV formulations provide more than sufficient plasma exposure necessary for antiviral activity**

**Based on plasma and PBMC/GI Bx viral load responses over the interval studied there does not seem to be an advantage to adding DRV**

**Starting from peak viremia in SIVmac239 infected Indian rhesus macaques, all animals could be suppressed to < 30 copy Eq/mL, but this required approximately 16 weeks of treatment**

**For unknown reasons the addition of DRV seems to decrease C24hr levels of DTG in the rhesus macaques**

**Substituting TDF for TFV significantly lowered plasma exposure of TFV which can be a safety advantage to minimize potential renal or other toxicity, especially with prolonged dosing**

**Frederick National Laboratory is accredited by AAALAC International and follows the Public Health Service Policy for the Care and Use of Laboratory Animals. Animal care was provided in accordance with the procedures outlined in the "Guide for Care and Use of Laboratory Animals" (National Research Council; 1996; National Academy Press; Washington, D.C.).**

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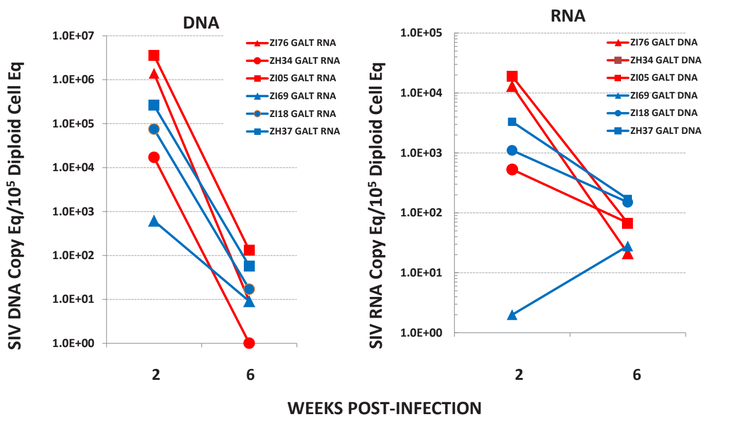
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*(separate study)*

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