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Supplementary Materials for

A long-acting integrase inhibitor protects female macaques from repeated high-dose intravaginal SHIV challenge

Chasity D. Andrews, Yun Lan Yueh, William R. Spreen, Leslie St. Bernard, Mar Boente-Carrera, Kristina Rodriguez, Agegnehu Gettie, Kasi Russell-Lodrigue, James Blanchard, Susan Ford, Hiroshi Mohri, Cecilia Cheng-Mayer, Zhi Hong, David D. Ho, Martin Markowitz*

*Corresponding author. E-mail: mmarkowitz@adarc.org

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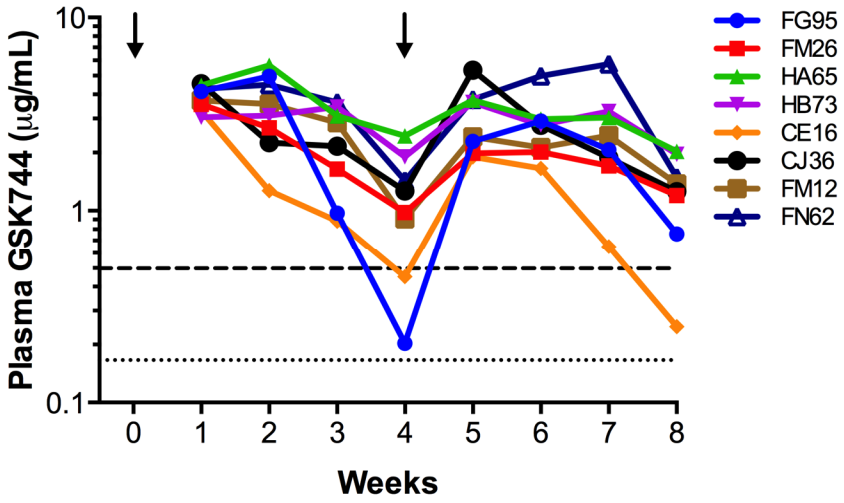
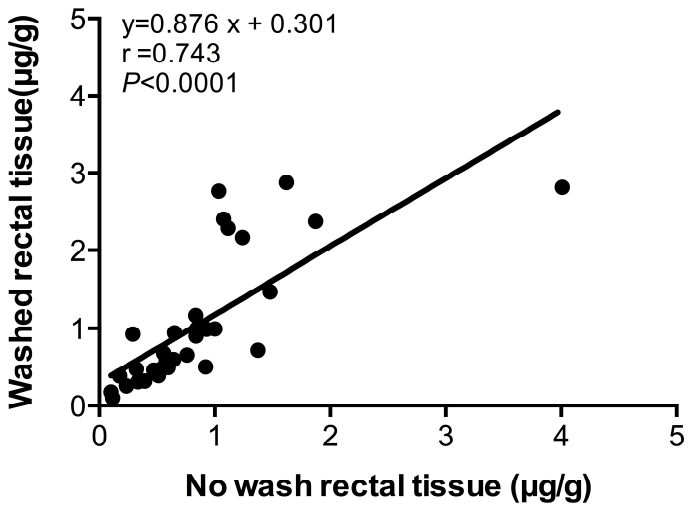
The PDF file includes:

Fig. S1.



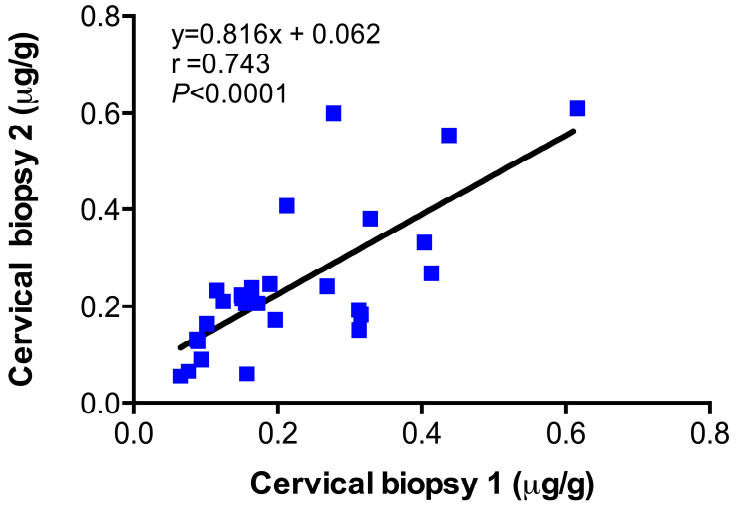
Plasma PK of individual GSK744 LA–treated rhesus macaques throughout the PK study. Eight female rhesus macaques were injected IM with 30 mg Depo-Provera on weeks -3 and 2, and with 50 mg/kg of GSK744 LA on weeks 0 and 4. Dotted and dashed horizontal lines represent 1x and 3x $PAIC_{90}$, respectively. LOQ >0.01 μg/mL

Fig. S2.



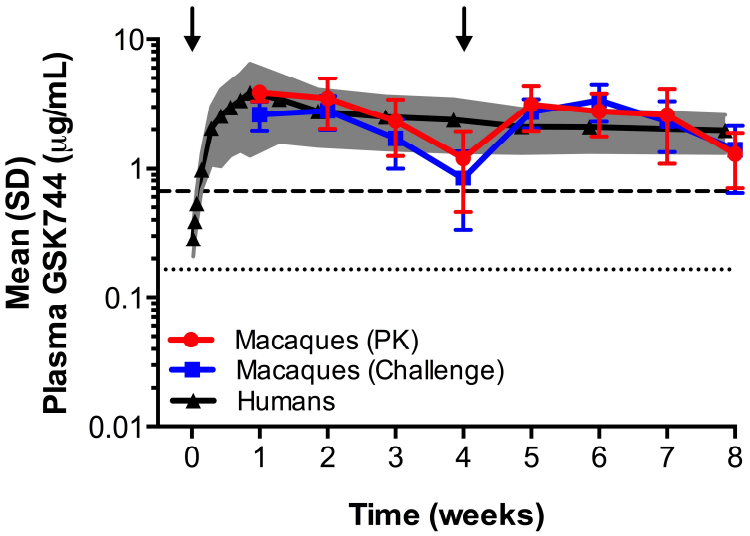
Correlation of rectal tissue GSK744 concentrations by processing method before freezing. Pinch biopsies (n=16-20) were collected on weigh paper at each time point. To examine the effect of washing the biopsies on GSK744 concentrations, half of the biopsies were rinsed in PBS, blotted dry, weighed and snap frozen. The other half of the biopsies were not subjected to PBS wash. The “no wash” biopsies were blotted to remove fecal contamination, as necessary, weighed and snap frozen. Each symbol represents rectal tissue concentrations from “washed” and “no wash” rectal tissue from an individual macaque at a given time point.

Fig. S3.



Correlation of cervical tissue GSK744 concentrations from individual samples. At each time point, two cervical biopsies were collected from an individual animal. Each symbol represents cervical biopsy concentrations from biopsy 1 and biopsy 2 from an individual animal. The average values were reported in Figs. 1B and 1D.

Fig. S4.



GSK744 plasma concentrations from Depo-Provera–treated rhesus macaques compared with humans. Rhesus macaques were administered 50 mg/kg GSK744 LA on weeks 0 and 4 as part of PK (n=8) or challenge study (n=8) and GSK744 plasma concentrations were overlaid with values from human volunteers (n=6) treated with 800 mg of GSK744 LA on week 0. Mean ± SD are shown. Dotted and dashed horizontal lines represent 1X and 4X $PAIC_{90}$, respectively.

Fig. S5.

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                  1         10        20        30        40        50        60
Consensus         FLEKIEPAQEEHDKYHSNVKELVFKFGLPRIVARQIVDTCDKCHQKGEAIHGQTNSDLGTWQMDCTHL
SHIV162P3stock    ............................................................
FG95W11           ............................................................
FG95W15           ............................................................
FG95W20           ............................................................
FM26W15           ............................................................
FM26W24           ............................................................
                   70        80        90       100       110       120       130
Consensus         EGKIIIVAVHVASGFIEAEVIPQETGRQTALFLLKLAGRWPITHLHTDNGANFASQEVKMVAWWAGIE
SHIV162P3stock    ............................................................
FG95W11           ............................................................
FG95W15           ............................................................
FG95W20           ............................................................
FM26W15           ............................................................
FM26W24           ............................................................
                  140       150       160       170       180       190       200
Consensus         HTFGVPYNPQSQGVVEAMNHHLKNQIDRIREQANSVETIVLMAVHCMNFKRRGGIGDMTPAERLINMI
SHIV162P3stock    ............................................................
FG95W11           ............................................................
FG95W15           ............................................................
FG95W20           ...........................................................G.......
FM26W15           ............................................................
FM26W24           ............................................................
                      210       220       230       240       250       260       270
Consensus         TTEQEIQFQQSKNSKFKNFRVYYREGRDQLWKGPGELLWKGEGAVILKVGTDIKVVPRRKAKIIKDYG
SHIV162P3stock    ............................................................
FG95W11           ............................................................
FG95W15           ............................................................
FG95W20           ............................................................
FM26W15           ............................................................
FM26W24           ............................................................
                        280       290  293
Consensus         GGKEVDSSSHMEDTGEAREVA
SHIV162P3stock    .......................
FG95W11           .......................
FG95W15           .......................
FG95W20           .......................
FM26W15           .......................
FM26W24           .......................
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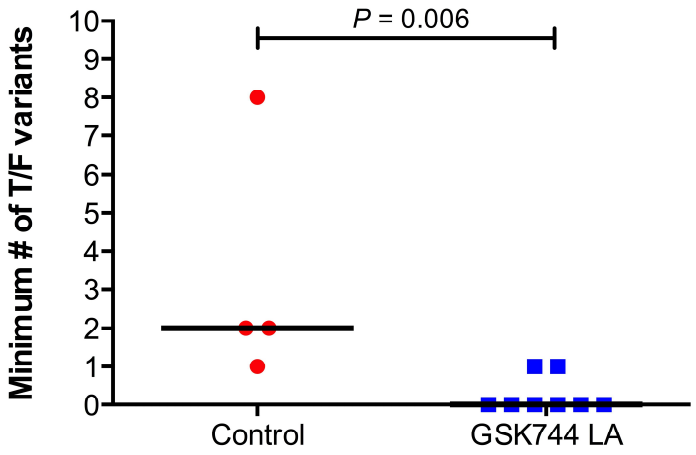
Consensus sequence analysis of SHIV integrase-coding regions from plasma of infected GSK744 LA–treated macaques.

Fig. S6.



Minimum number of T/F variants was estimated from plasma collected within 1 week of detection of viremia. Each point represents an individual macaque. Horizontal lines represent median for the group.

Table S1.

	Animal	Week detected		
		vRNA	Proviral DNA	Ab
GSK744 LA-treated	FG95	10	10	12
	FM26	14	14	16
Controls	CK97	2	2	5
	CK51	3	3	5
	CT22	2	2	4
	FC83	2	2	4

Summary of time of detection for plasma vRNA, proviral DNA, and anti-SHIV antibodies (Ab).

Table S2.

Recombinant virus	IC_{50} (nM)	IC_{90} (nM)
SHIV162P3 viral stock/FM26[a]	17.0	97.7
FG95	19.9	76.0
FG95 with E198G	20.4	91.4
FG95 with P142S	18.8	55.8
FG95 with P210V	17.6	93.3

[a]SHIV162P3 viral stock consensus sequence has the same integrase-coding sequence as FM26.

Susceptibility of single-cycle recombinant viruses with the integrase-coding regions of SHIV162P3 viral stock, FM26, FG95, and mutants to GSK744. IC_{50} = inhibitory concentration 50%; IC_{90} = inhibitory concentration 90%.

Table S3.

Animal	Treatment group	vRNA detected (week)	vRNA used for SGA (week)	Viral load at SGA (copies/ mL)	No. SGAs from vRNA	No. of hypermutated viral sequences	mean (range) of % nt diversity among SGSs	Estimated Minimum # of env variants in plasma
SHIV162P3 stock	NA	NA	NA	NA	25	0	0.242 (0-0.519)	NA
FG95	GSK744 LA	10	11	2.8×10^5	26	1	0.048 (0-0.170)	1
FM26	GSK744 LA	14	15	1.2×10^7	24	2	0.058 (0-0.160)	1
CK97	Control	2	3	1.8×10^5	24	0	0.052 (0-0.420)	2
CK51	Control	3	3	2.6×10^3	29	0	0.030 (0-0.091)	1
CT22	Control	2	3	2.6×10^4	30	0	0.303 (0-0.552)	8
FC83	Control	2	3	4.4×10^5	26	0	0.101 (0-0.325)	2

Env single-genome analysis summary.