Efficacy of Long-Acting Cabotegravir and Rilpivirine for PEP in a Macaque Model of RT SHIV Infection

NATIONAL CENTER FOR HIV, VIRAL HEPATITIS, STD, AND TB PREVENTION

Priya Srinivasan[1], Jining Zhang[1], Tiancheng Edwards[1], Chuong Dinh[1], Ayanna Green[2], Dawn Little[3], Tyana Singletary[1], Maria Mendoza[1], Yi Pan[1], Frank Deyounks[2], Ryan Johnson[4], Athena P. Kourtis[1], Walid Heneine[1], Gerardo Garcia-Lerma[1], James Smith[1]

[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]4ES Corporation, San Antonio, TX, USA,[3]Katmai Resource Management, LLC, Orlando, FL, USA, [4]Honnette LLC, Atlanta, GA

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BACKGROUND

- **Current PEP recommendations for non-occupational HIV exposures include 28 days of daily oral antiretroviral drugs**
- **Low adherence and inadequate regimen completion represents an important challenge**

We investigated in macaques if a single injection of long-acting cabotegravir and rilpivirine (CAB LA and RPV LA) could be an effective PEP regimen

METHODS

- **Clinically relevant doses of CAB LA (50 mg/Kg) and RPV-LA (100 mg/Kg)** administered intramuscularly to 6 rhesus macaques **24 hours post rectal exposure to RT SHIV**
- Infection outcome compared to **7 untreated controls**
- **Plasma CAB and RPV levels** monitored by LC-MS/MS
- **SHIV RNA in plasma** measured by RT-PCR
- **Seroconversion monitored by BioRad HIV-1/2 + O EIA** and by a **multiplex assay** specific for RT SHIV gag, pol and env

RESULTS

- **Median concentrations of CAB and RPV in plasma** during the first 28 days within clinically relevant levels (5,860, range= 2,130-15,650 and 64.5, range= 20-127 ng/mL, respectively)
- **All 7 untreated controls became SHIV RNA positive compared to 2/6 PEP treated animals (p=0.021, Fisher's exact test)**
- **Four of the six treated macaques aviremic and seronegative** during the entire follow up period (59 weeks)
- **No significant differences in plasma CAB or RPV concentrations** at weeks 1, 5, or 11 among breakthrough and non-breakthrough animals
- **Characteristics of breakthrough infections:**

Breakthrough 1:

» Transient low-level viremia between weeks 11 to 13 (range 327-2736 SHIV RNA copies/mL)

» Virus blips at week 33 and 45 (68 and 53 copies/mL, respectively)

» Seronegative by standard EIA assay

» Measurable responses to gag, pol and env by multiplex assay

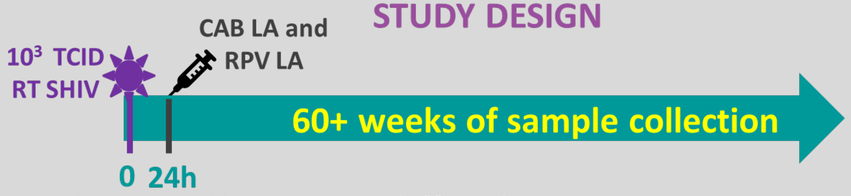
Breakthrough 2

» Detectable viremia between weeks 39 and 59 (range 53-1930 SHIV RNA copies/mL) when CAB and RPV were low or undetectable in plasma

» Seropositive by standard EIA and multiplex assay

- **Single dose of CAB LA and RPV LA given 24 hours after virus exposure provided clinical drug exposures but was only partially effective in our high dose rectal RT SHIV challenge model**
- **Late and transient detection of SHIV RNA in breakthrough infections is similar to findings in persons failing prophylaxis with CAB LA and highlights diagnostic challenges of this PEP modality**
- **Our results underscore the limitations of single-dose CAB LA and RPV LA use for PEP in humans**

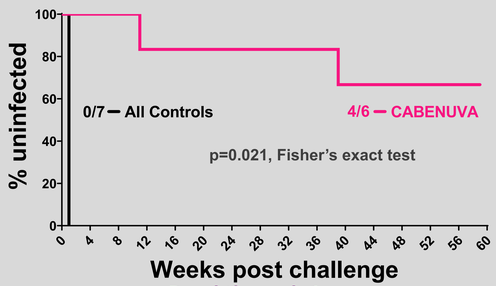
STUDY DESIGN



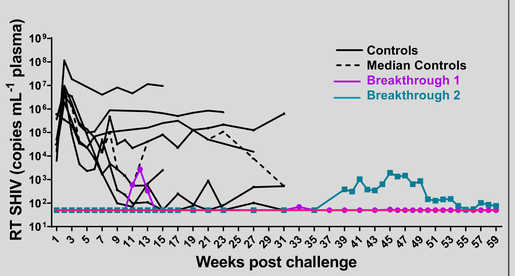
- Single rectal exposure to a high dose of RT SHIV ($10^{3.3}$ $TCID_{50}$)
- Clinically relevant doses of CAB LA (50 mg/Kg) and RPV-LA (100 mg/Kg) administered intramuscularly at 24h
- Samples: Blood (drug levels, viremia, provirus) and rectal secretions (viral shedding)

RESULTS

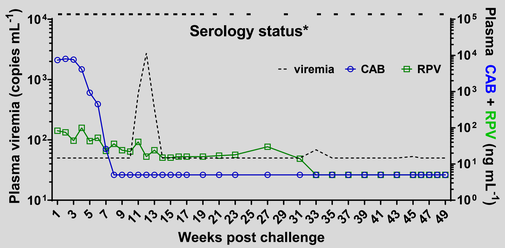
Kaplan-Meier plot



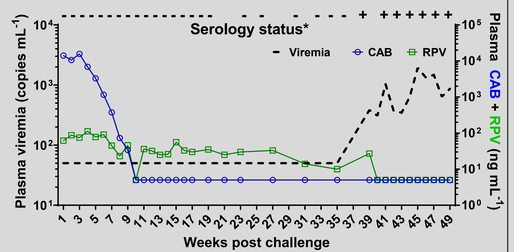
Plasma viremia



Breakthrough 1

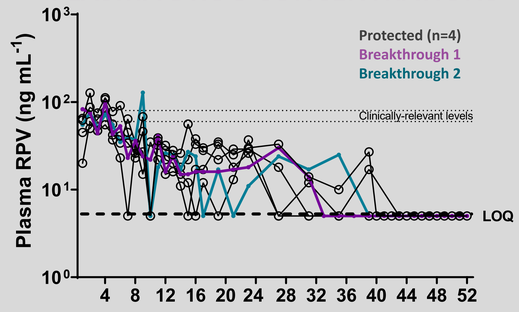


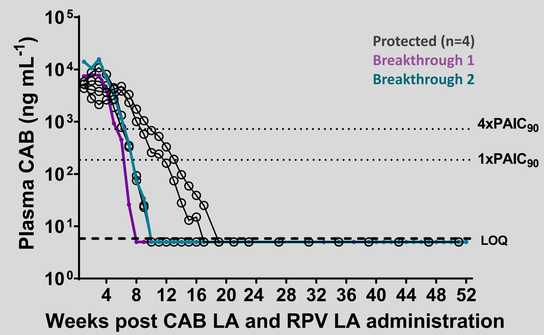
Breakthrough 2



*Antibody testing by BioRad HIV-1/2 + O EIA

PLASMA DRUG CONCENTRATIONS





PLASMA DRUG KINETICS

	Infected (n=2)	Uninfected (n=4)	p value**
CAB (ng/mL)*			
Week 1	10,743 (7,435-14,050)	5,238 (4,350-5,820)	0.064
Week 5	2,113 (930-3,295)	3,435 (1,865-4,470)	0.354
Week 11	5(5-5)***	123 (5-523)	0.273
RPV (ng/mL)*			
Week 1	73 (62-83)	50 (20-65)	0.165
Week 5	61 (43-78)	49 (37-56)	0.354
Week 11	39 (36-41)	27 (18-39)	0.165

* Median concentration (range) ** Kruskal-Wallis ***Undetectable

SEROCONVERSION BY SHIV-SPECIFIC MULTIPLEX ASSAY

Breakthrough 1

Weeks	p27	gp36	gp41	p66	gp130
9	-	-	-	-	-
11	-	-	-	-	-
13	-	-	+	-	+
15	-	-	+	-	+
17	-	-	+	-	+
19	-	-	+	-	+
21	-	-	+	-	+
23	-	-	+	-	+
27	-	+	+	-	+
31	-	+	+	-	+
43	-	+	+	-	+
45	-	+	+	-	+
46	-	+	+	-	+
47	-	+	+	-	+
48	-	+	+	-	+

Breakthrough 2

Weeks	p27	gp36	gp41	p66	gp130
31	-	-	-	-	-
39	+	-	+	-	+
40	+	+	+	-	+
41	+	+	+	-	+
42	+	+	+	+	+
43	-	+	+	+	+
44	+	+	+	+	+
45	-	+	+	+	+
46	+	+	+	+	+
47	-	-	-	+	+
48	-	+	+	+	+

Controls (n=3)

Weeks	p27	gp36	gp41	p66	gp130
3	+--	+-+	+-+	-++	+++
11	+--	+++	+-+	+++	+++
19	+--	+++	+++	+++	+++
27	+--	+++	+++	+++	+++

A highly sensitive multiplex assay using antigens matched to RT SHIV was used. Time of vRNA positivity in breakthroughs is highlighted.

CONTACT INFO: Priya Srinivasan, pvs6@cdc.gov

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