



## Background

Many HIV-related co-infections cause increases in plasma levels of HIV RNA, but a small number of agents (*Dengue virus*, *Orientia tsutsugamushi*, *Measles virus*) has been reported to cause transient decreases. During a recent measles outbreak in Uganda, we evaluated HIV viral dynamics in the affected participants of the Children with HIV and Malaria Project (CHAMP).

## Study Setting

CHAMP is an NIH-funded prospective, observational study examining interactions of HIV and malaria and their treatment in 300 HIV-infected Uganda children ages 1 to 10 years. CHAMP participants are evaluated in clinic for all febrile episodes. Any child who presented from June 1, 2006 to Jan 1, 2007 that was diagnosed with measles was included in this analysis. The WHO clinical case definition of measles was utilized: fever of  $\geq 38.0^{\circ}\text{C}$  with maculo-papular rash and at least one of: cough, coryza or conjunctivitis." (1)

## Measurements

Plasma HIV RNA viral load, absolute CD4 count, CD4%, and total lymphocyte count are determined routinely at 12 week intervals as part of the CHAMP protocol; an additional set of these laboratory values were obtained at the time of measles diagnosis. Age, antiretroviral therapy (ART) status and start date were determined using the CHAMP database.

## Analysis

Participants were divided into 2 subsets for analysis: ART-naïve subjects and those currently taking ART medications at the time of measles diagnosis. The laboratory values obtained on the most recent prior routine visit were designated "before"; those obtained on the day of diagnosis were considered "during"; those obtained on the subsequent routine visit were considered "after." Values from "before" measles were compared to those "during" and "after" using paired, 2-tailed Student's T-tests.

# Dramatic Reductions in HIV RNA among HIV-Infected Children with Acute Measles in Uganda

Theodore D. Ruel<sup>1</sup>, Jane Achan<sup>2</sup>, Anne F. Gasasira<sup>2</sup>, Edwin D. Charlebois<sup>1</sup>, Philip J. Rosenthal<sup>1</sup>, Grant Dorsey<sup>1</sup>, Moses R. Kanya<sup>2</sup>, Adeodata Kekitiinwa<sup>3</sup>, Joseph Wong<sup>1</sup>, Diane Havlir<sup>1</sup>, and the CHAMP team

1) University of California, San Francisco, USA; 2) Makerere University Medical School, Kampala, Uganda; 3) Baylor College of Medicine, Paediatric Infectious Diseases Clinic, Mulago Hospital, Kampala, Uganda

## Results

### ART-Naïve Participants

- 8 ART-naïve participants were diagnosed with clinical measles
- HIV RNA declined in all ART-naïve children, by a mean 1.4 log copies/ml ( $p < 0.0001$ )
- CD4 ( $p = 0.05$ ) and total lymphocyte counts ( $p = 0.15$ ) declined in most (6 of 7)
- CD4% remained stable
- Notably, the HIV RNA of patient 3 dropped 1.4 log despite a rise in CD4 and lymphocyte counts
- HIV RNA returned to prior levels following resolution of illness ( $p = 0.43$ )

### Participants on ART

- 7 participants on ART were diagnosed with clinical measles
- HIV RNA declined in all who had detectable viral loads ( $n = 3$ ) at baseline; however, recent ART initiation limits interpretation
- HIV RNA remained undetectable in those with undetectable virus at baseline ( $n = 4$ )

**Table 1. Viral Load and CD4 Before, During, and After Measles Illness**

P#	HIV RNA (copies/ml)			Log <sub>10</sub> (HIV RNA)				CD4 (cells/μl)			CD4%			TLC (x10 <sup>3</sup> cells/μl)		
	Before	During	After	Before	During	After	Δ†	Before	During	After	Before	During	After	Before	During	After
ART-Naïve	750,000	7,934	n/a	6.0	4.0	n/a	-1.98	173	85	n/a	5	4	n/a	4.4	2.5	n/a
2)	393,529	5,029	750,000	5.6	3.7	5.9	-1.89	411	369	437	34	23	33	1.2	1.6	1.4
3)	139,037	5,549	300,489	5.1	3.7	5.5	-1.40	835	935	631	35	34	30	2.6	3.5	2.1
4)	103,240	3,358	59,890	5.0	3.5	4.8	-1.49	n/a	527	559	n/a	16	20	2.5	3.2	2.5
5)	54,507	2,608	29,247	4.7	3.4	4.5	-1.32	1,295	749	1513	32	33	28	5.8	4.1	4.8
6)	43,802	3,932	49,227	4.6	3.6	4.7	-1.05	633	262	565	27	28	26	2.9	1.1	2.1
7)	29,068	1,261	54,402	4.5	3.1	4.7	-1.36	622	353	467	21	21	20	2.8	1.5	2.5
8)	10,093	3,573	13,372	4.0	3.6	4.1	-0.45	568	408	445	24	21	29	2.6	1.8	1.7
On ART	214,412	4,617	650§	5.0	4.0	3.0	-1.67	621	753	1010	11	21	27	5.7	3.9	3.8
10)	42,826	612	445*	5.0	3.0	3.0	-1.84	646	300	814	10	11	17	8.5	3.5	3.4
11)	3,905	618	n/a	4.0	3.0	n/a	-0.80	1,121	334	n/a	16	19	n/a	7.0	8.5	n/a
12)	<400	<400	<400	-	-	-	-	347	100	347	8	7	17	4.9	1.5	2.1
13)	<400	<400	<400	-	-	-	-	1,510	1068	1289	28	37	21	6.6	3.4	6.0
14)	<400	<400	<400	-	-	-	-	628	111	548	16	16	33	2.3	0.8	1.8
15)	<400	<400	<400	-	-	-	-	900	874	1435	31	32	35	3.2	3.4	4.0

TLC : total lymphocyte count

Before : 4 to 88 days prior to measles illness

During : on the day of measles diagnosis

After : 10 to 95 days after measles diagnosis

n/a : not available

† : "during" compared to "before"

§ : commenced ART 2 months prior to measles diagnosis

\* : commenced ART 10 months prior to measles diagnosis

## Discussion

Suppression of plasma HIV RNA by measles virus was first noted in a study of hospitalized children in Zambia by Moss et al.(2) However, without data prior to measles illness, their ability to quantify the suppressive effect and determine impact on baseline viral loads was limited. Our data, taking advantage of continuous monitoring of CHAMP participants, demonstrates the suppression of circulating HIV viral load by measles infection is universal and profound but transient. We further show that plasma viral load levels seem to return to equal, or even slightly elevated, levels following the resolution of illness.

Multiple mechanisms have been postulated to explain the decline in circulating HIV RNA seen with measles infection. Measles is well known to induce lymphopenia, suggesting a decline in HIV target cells as one potential mechanism. However, the reduction of HIV RNA of patient 3 despite a rise in CD4 and lymphocyte counts shows that the suppressive effect on HIV is not solely dependent on this mechanism.

Several circulating soluble immuno-mediators are elevated during measles infection, including RANTES, that provide alternative mechanisms for interference with HIV replication.(2) In vitro and ex vivo studies of measles virus have also demonstrated elevation in RANTES, MIP1- $\alpha$  and SDF-1 production; however, the greatest suppression in those assays depends on the presence of live measles virus.(3,4) Local effects at the tissue level and other soluble factors related to lymphoproliferation may be important. Further study of the mechanism of measles-induced HIV suppression may yield important insights into HIV pathogenesis that might be exploited in the development of future treatment strategies.

## References

- 1) www.who.int/immunization\_monitoring/diseases/measles\_surveillance
- 2) Moss, et al., Suppression of human immunodeficiency virus replication during acute measles. J Infect Dis, 2002. 185(8): p. 1035-42.
- 3) Garcia, et al., In Vitro Suppression of Human Immunodeficiency Virus Type 1 Replication by Measles Virus. J. Virol., 2005. 79(14): p. 9197-9205.
- 4) Grivel, et al., Inhibition of HIV-1 Replication in Human Lymphoid Tissues Ex Vivo by Measles Virus. J Infect Dis, 2005. 192(1): p. 71-78