ZIKA VIRUS CO-INFECTION AMONG HIV-INFECTED PREGNANT WOMEN IN A BRAZILIAN COHORT

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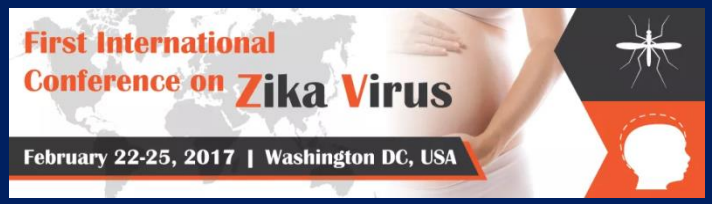

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Disclosure

No financial disclosure

Background

- ZIKA VIRUS – Arthropod-borne virus RNA Virus, Family *Flaviviridae*

- First isolation in Zika forest of Uganda, 1947

- First human cases – 1954, Nigeria → spread throughout Africa and Asia

- Three main epidemics – Yap Island (Micronesia 2007), French Polynesia (South Pacific 2013-2014) and then in the Americas in 2015

- Recently cases notified in West Africa, Singapure, Thailand and China

Background

- Globally, 1,600,000 suspected cases

- Main Vector in Americas – *Aedes aegypti and Aedes albopictus;* they may also transmit other arboviruses (Dengue, Chikungunya and Yellow Fever)

- In Brazil, Dengue is endemic; Sylvatic Yellow Fever is present; and there has been a recent outbreak of CHIKV

- From March 2015 to January 2017 128,266 confirmed cases of ZIKV infection in Brazil

Background

- The concurrence of these arbovirosis with similar clinical symptoms and the lack of rapid tests with good accuracy pose a challenge for the ZIKV diagnosis

ZIKV - Clinical Features

- Asymptomatic - 80%
- Main Symptoms:
  - Fever
  - Rash
  - Pruritus
  - Arthritis/arthralgia
  - Myalgia
  - Conjunctivitis
  - Fatigue

Didier Musso, *Clin Microbiol Rev*, 2016,
Brasil P*, NEJM*, March 2016

Complications

- Neurological

  Guillain Barré Syndrome

- Maternal/Neonatal outcomes

  Abortion

  Stillbirth, Prematurity

  Congenital syndrome associated with Zika virus infection (Microcephaly, Cerebral calcifications, ventriculomegaly)

Didier Musso & Duane Glube *Clin Microbiol Rev*, 2016
Brazil P et al, *NEJM*, 2016

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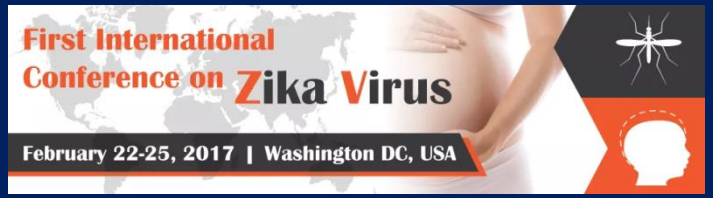

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Study Background

- Limited data - Impact of ZIKV infection in immunocompromised population

- In Brazil, 842,710 HIV/Aids cases notified[1]

- Few reports on ZIKV and HIV-coinfection in adults, infants, pregnant women and pregnancy outcomes[2-3]

1 MS SINAN *Boletim Epidemiologico* , Ano V,n.1, 2016,
2 Joao EC et al , *PIDJ*, 2016
3 Calvet G et al *J. C.lin. Virol*

Objectives

- Report the prevalence of ZIKV, CHIKV and DENV infection in a Brazilian cohort of HIV-infected pregnant women as a whole and in subgroups of asymptomatc and symptomatic patients

- Describe clinical features of ZIKV infection in this cohort

- Describe congenital syndrome associated with ZIKV infection in asymptomatic and symptomatic patients from this cohort

Methods

- Cohort of HIV-infected pregnant women in a referral PMTCT center in Rio de Janeiro (RJ)

- Prospective/retrospective

- Sociodemographic, clinical and laboratory maternal characteristics and infant outcomes

- Samples collected at first clinical visit and at 34-36 weeks of gestation. In addition samples were collected at anytime in the presence of any arboviruses infection related symptoms (fever, maculopapular rash, pruritus, anorexia and/or mialgia)

- The study was approved by the local IRB

Methods for Laboratory Analysis

- **Serological assays:**
  - Dengue IgG and IgM (Alere Medical Co., Japan)
  - Chikungunya IgG and IgM (Euroimmun, Germany)
  - Zika:
    - IgG and IgM (Chembio Diagnostic Systems, USA)
    - IgG: *in house* EIA assay using Zika NS-1 rec protein
  - Plaque Reduction Neutralization Test (PRNT)
    - Neutralizing antibodies against Zika and Dengue
- **Molecular assays:**
  - Dengue, Chikungunya and Zika: real time PCR*

*Lanciotti et al., *Emerg Infect Dis*, 13(5), 2007 and 14(8), 2008
Menting et al, *Advances in Virol*, 2011

Testing scheme

Blood samples tested for Dengue, Chikungunya and Zika IgG and IgM

- **Asymptomatic women (n=196)**
  - For 177 women two samples were collected in different time points (first sample, S1 and second sample, S2);
    - All S2 samples were tested for IgG and if:
      - Reactive: IgM on S2 tested and IgG and IgM tested on samples S1;
      - Non-reactive: only IgM tested on S2 samples.
  - For 19 women only one sample was available.
    - All samples tested for IgG and IgM

- **Symptomatic (n=23)**
  - Molecular assay was performed if plasma sample was collected within PCR detectable period (defined as two weeks after symptoms onset). If out of this period, serologies (IgG and IgM) and PRNT.

Results

- HFSE PMTCT Center – Jan 2015 - May 2016
- 219 pregnant women (196 asymptomatic, 23 symptomatic)
- Median maternal age – 26
- Median CD4 cell count at entry – 459 cells/mm^3
- Median HIV viral load log at entry – 4.60
- DENV serology positive – 193/219 (88%)
- Chikungunya serology positive - 9/219 (4.1%)
- ZIKV serology positive – 20/219 (9.1%)

Results

Clinical symptoms in symptomatic subgroup

Symptoms	Arbovirosis Symptomatic subgroup	ZIKV infection Symptomatic subgroup
	N=20	N=10
	%	%
Rash	95.0	90.0
Arthralgia/Arthritis	65.0	70.0
Pruritus	65.0	60.0
Fever	45.0	30.0
Myalgia	45.0	30.0
Fatigue	30.0	20.0
Headache	25.0	30.0
Conjunctivitis	25.0	20.0
Nausea	15.0	10.0

Results of diagnostic tests

	Confirmed ZIKV infection	Possible ZIKV infection	Others acute arboviral infections		No infection	Not conclusive
	PCR	Serology	DENV	CHIKV		
Symptomatic	5	5	2	8*	0	3**
Asymptomatic	0	10	7	2	17	160**

* 2 PCR positive

** Previous DENV infection (IgG only)

Data of symptomatic HIV pregnant women subgroup according to arbovirus types

Case N°	Arbovirosis recently	Type of Arbovirosis	First symptoms trimester	Age/year	CD4 count at entry (cells/mm^3)	HIV Viral Load at entry (copies/mL)	Congenital abnormalities	Gestacional age/weeks	Neonatal Gender
1	YES	ZIKV	1st	32	169	*	YES	20**	NA
2	YES	ZIKV	1st	20	500	*	YES	37	Male
3	YES	ZIKV	2nd	23	262	4.13	YES	37	Male
4	YES	ZIKV	1st	29	970	*	NO	40	Female
5	YES	ZIKV	1st	38	454	*	NO	39	Female
6	YES	ZIKV	2nd	22	1193	*	NO	39	Male
7	YES	ZIKV	2nd	20	638	2.72	NO	38	Female
8	YES	ZIKV	2nd	18	436	5.11	NO	38	Female
9	YES	ZIKV	3rd	31	103	3.22	NO	36 +5	Female
10	YES	ZIKV	1st	41	459	*	NO	39	Female
11	YES	CHIKV	1st	16	507	4.81	NO	38	Female
12	YES	CHIKV	1st	22	635	4.47	NO	39	Male
13	YES	CHIKV	1st	22	337	4.19	NO	39	Male
14	YES	CHIKV	1st	23	462	3.70	NO	38	Female
15	YES	CHIKV	1st	22	270	4.54	NO	34	Female
16	YES	CHIKV	2nd	19	652	4.10	NO	39	Female
17	YES	CHIKV	2nd	32	316	3.84	NO	38	Female
18	YES	CHIKV	3rd	31	404	*	NO	41	Male
19	YES	DENV	1st	31	840	2.79	NO	39	Male
20	YES	DENV	1st	23	833	*	NO	40	Female
21	NO	ND	2nd	28	119	5.85	NO	36 +3	Female
22	NO	ND	2nd	29	312	2.74	NO	39	Male
23	NO	ND	2nd	37	635	3.07	NO	39	Female

*Lower than detectable limit

**Abortion

Results

Description of congenital abnormalities

Patients	Cohort	Congenital abnormalies
Patient 1	symptomatic	Microcephaly, arthrogryposis and hydrops
Patient 2	symptomatic	Hydrocephalus, cerebral calcifications and meningomyelocele
Patient 3	symptomatic	Microcephaly, ventriculomegaly, cerebral calcifications and renal pyelectasis
Patient 4	asymptomatic	Microcephaly

Results

Congenital abnormalities in the patients with ZIKV

SYMPTOMS	CONGENITAL ABNORMALITIES		RR (IC95%)
	YES N (%)	NO N (%)	
SYMPTOMATIC	3 (30.0)	7 (70.0)	3.0 (0.372-24.171)
ASYMPTOMATIC	1 (10.0)	9 (90.0)	
TOTAL	4 (20.0)	16 (80.0)	

Study Limitations

- ZIKV diagnosis was performed in a population with a high prevalence of other arbovirosis
- Small sample size

Summary/Conclusion

- HIV-infected women who presented with ZIKV-related symptoms were more likely to have severe fetal/infant outcomes than asymptomatic ones and more studies should address this subset of population

- Congenital abnormalities may also occur in asymptomatic ZIKV infected pregnant women

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ALSO GRATEFUL TO ALL PREGNANT WOMEN AND THEIR INFANTS