EPIDEMIOLOGICAL AND CLINICAL FEATURES OF MEASLES IN A COHORT OF HIV-1 INFECTED ADOLESCENTS, DURING A RECENT MEASLES OUTBREAK IN ROMANIA

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Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Background (1)

- Measles remains an important cause of child mortality (12.2% of the children with HIV-1 as compared to 4.3% of non-HIV-1-infected children)
- Outbreaks occurred in countries with a high HIV-1 prevalence (Chad, Nigeria, and Zimbabwe)
- Failure in maintaining high measles vaccine coverage

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Background (2)

- A decreased amount of measles antibodies in mothers, low titres of transferred maternal antibodies and a poor response to vaccination (only 33% of the children with HIV-1 maintained measles IgG antibodies)
- WHO recommended that infants receive two doses of measles vaccine, at 6 and 9 months
- HAART should be administered to children and adults prior to measles vaccination

Source: WHO/UNICEF estimates of national immunization coverage [online database]
Geneva, World Health Organization, 2009
Estimates based on data available up to December 2009
Characteristics of HIV-1 infected children from Romania

- Parenterally infected with HIV-1 subtype F-1 in the first years of life (1987-1989)
  - Homogenous group
  - Current age of 20-22 years
  - HAART starting 1998

- Group with severe immune suppression
  - Multiexperienced HAART with low adherence
  - Newly diagnosed

- Immunizations?

- Coinfection with HBV (60%)

- Experienced three measles outbreaks

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Measles epidemics in Romania

- measles vaccination coverage 97%

but

European sero-epidemiology network 2 (ESEN) 2001-2002 reported
- 89% - general prevalence of measles antibodies
- in children < 5 years → 39% (430,000) of children had no protective antibodies

accumulation of critical (receptive mass) → measles outbreak Oct 2005 - new vaccination group (7-11 months)¹

viral genotype D4 was identified during 2005-2006 measles outbreak²

¹ Romanian Ministry of Health²
MMWR 2006; 55 (50:1348-1351)

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Incidence of newly diagnosed measles cases in Romania

Currently National Vaccination Programe recommed measles vaccination at age of 10-15 months and 7 years

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# Romanian national vaccination programme

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 hours</td>
<td>Hep B</td>
</tr>
<tr>
<td>4-7 days</td>
<td>BCG</td>
</tr>
<tr>
<td>2 months</td>
<td>DTP - Hep B, VPO</td>
</tr>
<tr>
<td>4 months</td>
<td>DTP, VPO</td>
</tr>
<tr>
<td>6 months</td>
<td>DTP - Hep B, VPO,</td>
</tr>
<tr>
<td>12 months</td>
<td>DTP, VPO</td>
</tr>
<tr>
<td>12-15 months</td>
<td>MMR</td>
</tr>
<tr>
<td>30-35 months</td>
<td>DTP</td>
</tr>
<tr>
<td>7 years (1st grade)</td>
<td>DT, measles</td>
</tr>
<tr>
<td>9 years (3rd grade)</td>
<td>VPO, Hep B</td>
</tr>
<tr>
<td>14 years (8th grade)</td>
<td>DT, Rubella**</td>
</tr>
<tr>
<td>18 years (12th grade)</td>
<td>Hep B</td>
</tr>
<tr>
<td>Medical students, health-care workers</td>
<td>Hep B</td>
</tr>
</tbody>
</table>

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Measles antibodies prevalence in HIV-1 infected children from VBH during the last epidemics (2005-2007)

- 442 children included with at least one measurement of measles IgG

General characteristics of the patients:
- median age 17 years, range 0.2-21
- sex ratio F/M=211/231

Prevalence of positive measles IgG antibodies

- IgG neg 61.8%
- IgG poz 38.2%

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## Relationship between measles IgG Ab and CD4 count

<table>
<thead>
<tr>
<th></th>
<th>IgG pos</th>
<th>IgG neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4&lt;200</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>CD4&gt;200</td>
<td>137</td>
<td>218</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>273</td>
</tr>
</tbody>
</table>

$\chi^2=0.051$, p=ns

- Median CD4 count at IgG pos group 444 lf/mmC
- Median CD4 count at IgG neg group 415 lf/mmC

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There was no correlation between the no of vaccine doses, positive IgG and/or the CD4 count.
Longitudinal evaluation

- 119 children with negative baseline measles IgG Ab
- Median age 17 years (range 0.2-20)
- Median time frame between first and second evaluation 184 days
- Median CD4 count (397 lf/mm
c baseline, 391 lf/mm
c at moment of second evaluation)

First evaluation

- 68 IgG pos

2nd evaluation

- 23 response to measles vaccination
- 22 measles
- 119 pts IgG neg
- 51 IgG neg

- 23 seroconversion in the absence of clinical signs of measles
- 13 pts CD4>200
- 10 pts CD4<200

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Our experience (VBH) with measles in infants (<1 year) during the previous measles epidemics (2005-2006)

Measles in babies with perinatal exposure to HIV-1

- 3 children born to HIV-1 positive mothers (2 with undetectable HIV RNA) were diagnosed with measles at age of 3, 4 and 12 weeks

- At the moment of clinical signs of measles:
  - 2 babies had positive IgM antibodies
  - 1 baby had initial negative IgM → became positive at a 2\textsuperscript{nd} testing (9 days later)
  - None of the 3 babies had positive IgG – however 2 of the 3 mother tested positive for measles IgG (babies were not breastfeded)

Presented at the 3\textsuperscript{rd} HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Response to vaccination in children with CD4>200 lf/mm during measles epidemics

114 pts with neg IgG ab received measles vaccine

47 pts retested for IgG after a median of 172 days (range 91-420)

19 seroconversion

24 IgG neg

Revaccination 9 pts

7 pts reevaluated median per 126 days

2 seroconversion

4 IgG neg

Revaccination 4 pts

4 pts reevaluated median per 60 days

2 seroconversion

2 IgG neg

The overall response rate to measles vaccination/revaccination during epidemics was 48.9%

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Measles in children with severe immune suppression (1)

Clinical features

- **Exanthema**: short period, particular aspect, may be absent
- **Koplick spots**: present even without rash, prolonged, extension

Complications: frequent, severe, high mortality ¹

Reinfection possible ² ³

Atypical measles

¹Kaplan LJ et al. JAMA 1992;267:1237-1241
Measles in children with severe immune suppression (2)

- Ineffective antibody levels after vaccination in HIV-1 infected children¹
  - Antibodies response to a single dose measles vaccine: 25-37%
  - Antibodies response to second dose vaccine: 50-66 %

- 25% measles antibodies prevalence in HIV-1 infected children in Romania²

- Impairment of naïve and memory cells responses to measles in HIV-1 infected children³

- Absence of Ig M antibodies
  - Measles without IgM but high/increasing IgG levels
  - Does not confirm measles diagnosis

- Prolonged virus shedding (31-60 days)⁴

¹Moss JW et all; CID 1999;29:106-112
²Cernescu et al; Rev Roum Virol 1990;41:133-134

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The last measles epidemics in HIV-1 infected children from VBH

- 41 children with clinical features of measles
  + 8 children with measles complications in the absence of any clinical signs of measles

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
# General data on HIV-infected children with measles (n=41)

<table>
<thead>
<tr>
<th>No. patients</th>
<th>17.3 years (Limits 0.2-18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td><strong>17.3 years (Limits 0.2-18)</strong></td>
</tr>
<tr>
<td><strong>Sex ratio</strong></td>
<td>M/F= 20/21</td>
</tr>
<tr>
<td><strong>HIV transmission route</strong></td>
<td>parenteral vertical</td>
</tr>
<tr>
<td><strong>Social background:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Classification of HIV infection (CDC)</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Immunological</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>HAART</strong></td>
<td>Ongoing N=36</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stopped</td>
<td>3</td>
</tr>
<tr>
<td>Without HAART</td>
<td>2</td>
</tr>
</tbody>
</table>

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Signs and symptoms at onset (n=39*)

- Fever: 39
- Cough: 39
- Coryza: 37
- Conjunctivitis: 34
- Anorexia: 29
- Malaise: 27
- Diarrhea: 8
- Oedema: 7
- Dysphonia: 7

* In 2 patients measles was diagnosed in other medical services

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### Characteristics of measles in a group of 39 children with complete evaluation

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Number</th>
<th>% of all pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4&lt;200 lf/mmc</td>
<td>20</td>
<td>51.3%</td>
</tr>
<tr>
<td>CD4&gt;200 lf/mmc</td>
<td>19</td>
<td>58.7%</td>
</tr>
<tr>
<td>Exanthema</td>
<td>35</td>
<td>89.7%</td>
</tr>
<tr>
<td>- Typical</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>- Discreet</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>- Atypical (upper limbs)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enanthema</td>
<td>31</td>
<td>79%</td>
</tr>
<tr>
<td>Positive IgM Ab</td>
<td>30</td>
<td>75.4%</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>30</td>
<td>76.9%</td>
</tr>
<tr>
<td>Measles pneumonia</td>
<td>4</td>
<td>10.2%</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>ADEM</td>
<td>3</td>
<td>7.6%</td>
</tr>
<tr>
<td>SMME</td>
<td>6</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

### Characteristics of measles in a subgroup of 20 pts with severe immune suppression

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>No. of pts.</th>
<th>% of pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exanthema</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>- Typical</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>- Discreet</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>- Atypical (upper limbs)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Enanthema</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>Positive IgM Ab</td>
<td>13</td>
<td>6.5</td>
</tr>
<tr>
<td>Seroconversion (n=17)</td>
<td>12</td>
<td>70.5</td>
</tr>
<tr>
<td>Measles pneumonia</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>ADEM</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>SMME</td>
<td>6</td>
<td>30</td>
</tr>
</tbody>
</table>

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Enanthema (Koplik spots)

- Present at 31 pts (79%)
- Mean duration: 2.8 days (limits 1-6 days)
- Extensive at 12 pts
- Delayed onset (after rash) 6 pts

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Atypical measles rash (upper limbs)

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Laboratory diagnosis

- IgM + at diagnosis - 30/41 (75.4%)
- IgM neg at diagnosis - 11 children
  - There was no significant difference in CD4 count at the moment of diagnosis for IgM pos pts vs IgM neg pts
- IgG + at diagnosis 14/41 (34%)
IgM negative patients with clinical features of measles

11 children
IgM negative

- 2 with measles confirmed by RT PCR from pharyngeal swabs (Deceased with measles pneumonia)
- 3 positive IgG Ab baseline increasing thereafter
- 6 positive IgM pts on a second/third determination after a median time of 35 days

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Laboratory diagnosis

- RT-PCR for measles from pharyngeal swabs
  - was positive in 11/11 patients tested at 1-6 days after clinical onset
  - has confirmed measles in 2 IgM negative pts *

*courtesy of dr. Lupulescu E “Cantacuzino”Institute Bucharest
Pos control  Neg control

1 2 3 4 5 6 7

400 bp

courtesy of dr. Lupulescu E “Cantacuzino” Institute Bucharest

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Changes in HIV infection immune and viral markers before and at measles onset

<table>
<thead>
<tr>
<th></th>
<th>Baseline N=37</th>
<th>Measles N=38</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 If/mmc (median)</td>
<td>309</td>
<td>206</td>
<td>NS</td>
</tr>
<tr>
<td>CD8 If/mmc (median)</td>
<td>862</td>
<td>504</td>
<td>NS</td>
</tr>
<tr>
<td>CD4/CD8 (median)</td>
<td>0.37</td>
<td>0.45</td>
<td>NS</td>
</tr>
<tr>
<td>HIV RNA c/ml log 10 (mean ± SD)</td>
<td>3.93 ± 1.42</td>
<td>2.91 ± 0.77</td>
<td>0.001</td>
</tr>
<tr>
<td>HIV RNA c/ml log 10 in pts with severe immune suppression</td>
<td>4.53 ± 1.20</td>
<td>3.33 ± 0.90</td>
<td>0.004</td>
</tr>
<tr>
<td>HIV RNA c/ml log 10 in pts with median immune suppression</td>
<td>3.24 ± 1.36</td>
<td>2.48 ± 0.16</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- median CD4 decline during acute measles episode = 25 If/mmc
- 8 pts with CD4>200 If/mmc became severe immune suppressed

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Comparison between HIV RNA values before and at measles episode

Log10 HIV RNA (c/ml)

HIV_RNA_before_measles  HIV_RNA_at_measles_episode

P = 0.001

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Respiratory complications

**Measles pneumonia** (presumptive diagnosis): 4 pts

- Severe immune suppression (CD4= 1,7,22,55)
- Onset at 4-8 days after rash
- Clinical features:
  - Acute respiratory failure
  - Diffuse bilateral crackling sounds (2 pts) normal auscultation (2 pts)
  - Rapid decrease of pO2
  - Increase of LDH
- Differential diagnosis with bacterial pneumonia, PCP
Immune and viral markers of HIV infection in patients with measles pneumonia

CD4 count before and at measles onset in patients with measles pneumonia

HIV RNA before and at measles onset in patients with measles pneumonia

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Radiological findings (BM)

3rd day after rash

5th day after rash

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Radiological findings (CA)

3rd day of rash

4th day of rash

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Radiological findings (ZR)

1st day of fever

6th day, no rash, enanthema present

7th day no rash, no enanthema

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Neurological complications of measles

- Acute encephalitis <1 month – autoimmune mechanism
- Measles inclusion body encephalitis (MIBE) 1-12 months (in immune suppressed patients)
  - Cognitive impairment
  - Seizures
  - Deaths >80%
  - 4 HIV-infected patients with MIBE reported in English-language literature (2 in children)

- Subacute sclerosing panencephalitis (SSPE) > 2 years after acute infection
Epilepsia Partiala Continua (EPC) in VBH

Occurred in 1997-1998 (context of measles epidemics)
22 pts from VBH and in 2005-2006 in 14 patients. Total patients = 36

- Clinical particular features: Identical pattern
- Onset after a median period of 120 days (limits: 35-305) from measles contact
- 8 pts - no clinical evidence of measles episode
- Uncharacteristic measles episode:
  - absence of rash in 3 pts
  - rash at upper limbs (atypical?) 1 pts
  - negative IgM measles antibodies at episode in 3/5 pts
- Low CD4 count: median 18 (limits: 1-231) l/mc

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Clinical diagnosis

- Presence of myoclonic jerks at limbs and/or face in all patients
  - initially unilateral myoclonic jerks of one body part
  - rapid extent (2-8 weeks) either involving other muscle groups from the same or the other side of the body
  - continuous pattern ~ epilepsia partialis continua in 5/10 pts
- initially preserved mental status - 8 pts
- motor impairment was absent or mild at onset but weakness and plegia have been noticed afterwards at all patients on initially myoclonical limbs
- coma after a median of 19 days (1-24)
- fatal outcome after a median time of 24 days (5-26 days)

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Serological evaluation at EPC

<table>
<thead>
<tr>
<th>Measles antibodies</th>
<th>plasma</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>pts</td>
<td>IgM</td>
<td>IgM</td>
</tr>
<tr>
<td>CR</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>DI</td>
<td>pos</td>
<td>-</td>
</tr>
<tr>
<td>DR</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>MS</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>MA</td>
<td>neg</td>
<td>pos</td>
</tr>
<tr>
<td>RM</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>ST</td>
<td>neg</td>
<td>pos</td>
</tr>
<tr>
<td>TD</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>CC</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>JF</td>
<td>neg</td>
<td>pos</td>
</tr>
</tbody>
</table>

- serological screening for other viruses & Tx were inconclusive

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Neuroimaging

Child with epilepsy partialis continua (EPC)
Diagnosed with measles subacute encephalitis during measles epidemics 1997-1998

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
MRI at onset of myoclonic jerks (EPC) at a 16 year old patient with encephalitis 53 days after presumed measles episode (sine exanthemate, negative IgM antibodies) but with positive cultures for measles from blood.

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
MRI aspects in a 17 year old adolescent with encephalitis and EPC

At onset of myoclonic jerks (EPC)-125 days after uncharacteristic measles episode

20 days after EPC Important extent of initial lesions

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Electroencephalography showed diffuse slow waves and localized spike-waves.
Measles in the HIV brain

Immune cytochemistry using a measles monoclonal antibody identified many positive cells in the brain of a pediatric HIV infected patient who died with seizures. (Original mag. 20X)

Courtesy of prof. Cristian Achim - University of California San Diego

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Survival in patients with SMME based on the degree of immune suppression at the moment of diagnosis.

- CD4<200 lfm/mmc
- CD4>200 lfm/mmc

36 children with SMME during the last 2 measles epidemics
Mortality rate 100%
Case definition *Measles subacute myoclonic encephalitis*

- **Presumptive diagnosis**
  - Epidemiologic: previous measles episode (2-12 mths or presumed contact with measles virus (during measles outbreak))
  - Clinical features:
    - initially unaltered mental status
    - unilateral myoclonia consequently associated with motor deficit and extension to the other side of the body
    - rapid progression to death
  - Neuroimaging (high T2 and FLAIR signal areas)

- **Definitive diagnosis:** immune cytochemistry exam
  - PCR CSF ?

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Subacute sclerosing panencephalitis (onset in dec 2006)

<table>
<thead>
<tr>
<th>Measles Ab reactivity</th>
<th>30-Jan-06</th>
<th>24-Apr-07</th>
<th>13-Feb-09</th>
<th>20-May-09</th>
<th>30-Jul-09</th>
<th>14-Jan-10</th>
<th>22-Jun-10</th>
<th>8-Dec-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum</td>
<td>6.3</td>
<td>5.98</td>
<td>over</td>
<td>3.46</td>
<td>3.65</td>
<td>poz</td>
<td>N/A</td>
<td>11.04</td>
</tr>
<tr>
<td>CSF</td>
<td><strong>4.3</strong></td>
<td><strong>4.84</strong></td>
<td>over</td>
<td><strong>2.56</strong></td>
<td><strong>4.06</strong></td>
<td>poz</td>
<td><strong>11.28</strong></td>
<td><strong>12.6</strong></td>
</tr>
</tbody>
</table>

| CD4 (lf/mmc)          | 476       | 311       | 357       | 380       | 425       | 522       | 510       | 283     |
| CD8 (lf/mmc)          | 2550      | 1864      | 1666      | 1695      | 1675      | 2057      | 1860      | 1034    |
| HIV RNA plasma        | 119000    | <40       | <400      | <400      | <47       | <47       | <20       | <20     |
| HIV RNA CSF           | 1330000   | <40       | <400      | <400      | <20       | <47       | <20       | <20     |

- Single IgG oligoclonal band in CSF
- ↑ IgG index & IgG/alb
- Normal alb index

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Subacute sclerosing panencephalitis?

Sep 2007
Dec 2010

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
The coverage for measles in HIV-1 infected children is low (infants exposed from positive mothers and also in children who acquired infection after birth)

Even with adequate immunization, the immune response may be absent or ineffective

Measles diagnosis may be difficult or overlooked because of atypical or absent exanthema and an inconclusive serological profile (PCR confirmation ?)
Summary

- Neurological and respiratory complications have been frequent and severe in immune depressed children.
- We described a particular clinical entity in neurological complications of measles of children with severe immunodepression that we named: Myoclonic subacute measles encephalitis.
- Establish a connection between myoclonic jerks and measles.
- Investigating the immune impairment (HIV or other causes).

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy.
Medical team