Studies on HIV-exposed uninfected individuals in Asia and Africa: Lessons learned

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Regulation of Retroviral Infections Unit

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Nobel Prize 2008
Synopsis

1. Correlates of protection against HIV-1 infection arisen from our studies on EU

2. Issues in researches on HIV-exposed uninfected individuals
### VIETNAM

**EU: IDU**  
(45: 38 M, 7 F)  
Age (m): 47 y  
**Risk factor:**  
Shared needles - drug use: 13-31 years  
**Serology:**  
HBV: 82%  
HCV: 100%  
HTLV: 80%  
**Controls:**  
Blood donors (50)  
HIV+ IDU (10)

### CAMBODIA

**EU: Partners of HIV+ individuals**  
(48: 7 M, 41 F)  
Age (m): 32 y  
**Risk factor:**  
Unprotected sex intercourses. Common life > 1.5 y from seroconversion  
**Controls:**  
Blood donors (50)

### CAR

**EU: Partners of HIV+ individuals**  
(45: 20 M, 25 F)  
Age (m): 35 ans  
**Risk factor:**  
Unprotected sex intercourses. Common life: 8 ans  
**Controls:**  
Blood donors (46)

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Truong XL et al. AIDS 2003  
Capolulade-Metay C. et al. AIDS 2004  
Tran H.K et al. AIDS Res Hum Retrov 2006  
Saez-Cirion A. et al, Retrovirology 2006  
Nguyen M et al, J AIDS 2006  
Lopalco L et al J Gen Virol 2005  
Bégaud E. et al. Retrovirology 2006
HYPOTHESIS:
Early mechanisms of protection against HIV infection

- Cell resistance to HIV infection?
- Innate immune response?
CELL SUSCEPTIBILITY TO *IN VITRO* HIV-1 INFECTION
PBMC resistance to HIV-1 *in vitro* infection

**RESISTANCE:** p24 reduction > 1 log

*Truong XL et al. AIDS, 2003*
Resistance to R5 viruses

When the virus does not find the key..

When the virus finds the door locked..

**Enhanced sensitivity to β-chemokines**

**CCR5 heterozygous mutations**

**Sáez-Cirión A. et al, Retrovirology, 2006**
Pantropic resistance to HIV-1

When the virus finds an intracellular block …

Restriction independent of HIV-1 co-receptors
Other retroviruses affected

Sáez-Cirión A. et al, Retrovirology, 2006
Resistant CD4 T cell clones from EU W276

Conserved restriction phenotype  HIV-permissive heterokaryons

Lack of a cellular co-factor to retroviral replication?
INNATE IMMUNE RESPONSE
NK CELL ACTIVITY AND REPERTOIRE
Increased NK cell activity in Vietnamese EU

Cytotoxicity

* P < 0.01

IFN-γ

* P < 0.01

Constitutive activation of NK cells in Vietnamese EU

NK cells from EU may be armed \textit{in vivo} to generate a rapid and effective response to HIV-1.
Peculiar NKR repertoires in Vietnamese EU

- High KIR3DS1/KIR3DL1 ratio
- Conserved expression of NKp30

- Heterogeneity in NKR repertoires among EU
- Balance of NKR expression in favor of NK cell activation

Ravet S. et al, Blood 2007
Conclusions

The apparent resistance to HIV-1 infection in Vietnamese EU is associated to:

- Restricted replication of HIV-1 in CD4+ T cells
- High HIV-1 suppressive capacity of CD8+ cells
- High constitutive activation of NK cells

Multiple mechanisms may contribute to the natural protection against HIV-1:

- Reduced susceptibility of target cells to HIV-1
- Innate anti-viral defences by activated CD8+ and NK cell compartments
ISSUES IN RESEARCH
ON HIV EXPOSED UNINFECTED INDIVIDUALS
FOLLOW-UP AND EXPOSURE: AN INTRINSIC CONTRADICTION

Medical counseling and prevention = no more exposure

• In Cambodia: 93% of the serodiscordant couples at the second visit, 6 months after the recruitment, declared having safe sex

• In Vietnam: after a Government campaign for prevention most IDU in HCMC declared using disposable syringes
VULNERABILITY AND FOLLOW-UP: POTENTIALLY CONFLICTING

- Risk of high levels of loss to follow-up may hamper cohort studies on vulnerable groups of individuals such as IDU or sex workers
- Studies on vulnerable groups may raise ethical concerns
ARE EU REALLY RESISTANT TO INFECTION?

Non infected by chance or by natural protection?

Cumulative risk of being HIV-infected by their infected spouse *:

**CAR** (2-3 intercourses per week, 8 years common life)

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<tr>
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<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>1 year</td>
<td>9.1%</td>
<td>13.4%</td>
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<tr>
<td>8 years</td>
<td>53.5%</td>
<td>68.3%</td>
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**Cambodia** (1-2 intercourses per week, 1.5-3 years from seroconversion)

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<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>1.5 years, 1 intercourse/w</td>
<td>6.1%</td>
<td>8.9%</td>
</tr>
<tr>
<td>3 years, 2 intercourses/w</td>
<td>22.1%</td>
<td>31.2%</td>
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*probability of infection per unprotected heterosexual sexual intercourse: 0.0008 for men, and 0.0012 for women

*Courtesy of A. Fontanet, Institut Pasteur*
WILL GENETIC STUDIES ON EU BE CONCLUSIVE?

• Small size populations: too low power in genetic analysis, and especially GWA studies

• Genetic diversity in EU from distinct countries/ethnicities: major concern for meta-analysis or for gathering different groups in one study
SPECIFIC PROBLEMS FOR RESEARCH IN DEVELOPING COUNTRIES

• Infrastructural issues:
  – Taking and conservation of biological samples
  – Training of scientific and technical staff

• Socio-political issues:
  – Difficulties due to National or local policies towards AIDS and/or at risk groups
  – Political instability
In spite to these problems and limits, and to try to overcome some of them

WELCOME TO THE
NATURAL IMMUNITY CONSORTIUM
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