Historical Perspective of HIV-exposed Seronegative Individuals (ESN): Has nature done the experiment for us? (Notes from the 20th century)

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First report of T cell responses in PBMC of HIV-exposed, Ab-negative individuals:

T cell responses towards HIV in infected individuals with and without zidovudine therapy, and in HIV exposed sexual partners.
A Ranki et al. AIDS 1989; 3: 63-9
Abstracts from Winnipeg group (1990-93)


M Clerici et al. T helper cell assays detect exposure to HIV-1 antigen earlier than demonstration of infection by serum antibodies or polymerase chain reaction. Abst # WA 76

Question

If HIV-specific cell-mediated immunity (CMI) can be detected in HIV-exposed individuals before seroconversion,....

Can HIV exposure result in CMI without detection of serum Ab?
... also from the Florence AIDS Conference

JV Giorgi et al. HIV-specific cellular immunity in high-risk HIV-1 seronegative homosexual men. Abst # WA 120

M Clerici et al. Specific T cell immunity to HIV-1 envelope peptides in seronegative individuals with recent exposure to HIV-1. *J Infect Dis.* 1992; 165: 1012-9
ESN generate T helper cell responses to HIV antigens

Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya

Keith R Fowke, Nico J D Nagelkerke, Joshua Kimani, J Neil Simonsen, Aggrey O Anzala, Job J Bwayo, Kelly S MacDonald, Elizabeth N Ngugi, Francis A Plummer

*The Lancet.* 1996; 348: 1347-51

**Conclusion:**
A small percentage of highly exposed, seronegative prostitutes appear to have natural protective immunity to HIV-1 infection.
ESN generate HIV-specific CTL responses


ESN are found among intravenous drug abusers

W Barcellini et al. *In vitro* production of type 1 and type 2 cytokines by peripheral blood mononuclear cells from high-risk HIV-negative intravenous drug users. *AIDS*. 1995; 9: 691-4
Prior to the use of antiretroviral therapy in pregnant women, vertical transmission of HIV (maternal→fetal/perinatal) transmission was 25-30%.

Neonates (70-75%) who did not become HIV infected comprise an ESN cohort that was continuously exposed.

Are neonates who escaped vertical transmission examples of ESN?
Newborns of HIV-infected mothers can generate T helper and CTL responses to HIV antigens

M Clerici et al. Cellular immune factors associated with mother-to-infant transmission of HIV. AIDS. 1993; 7: 427-33


HIV-specific cytotoxic T-cell activity in an HIV-exposed but uninfected infant

Sarah L. Rowland-Jones
Douglas F. Nixon
Marian C. Aldhous
Frances Gotch
Koya Ariyoshi
Nicholas Hallam
J. Simon Kroll
Karin Froebel
Andrew McMichael

Lancet 1993; 341: 860-1

The diagram shows the percentage lysis of different cell cultures.

CTLs from the baby recognise HLA-B8-restricted antigen in HIV gag.
Mucosal IgA antibodies in ESN

Anti-HIV soluble factors in ESN


What is the minimum number of HIV exposures required to induce CMI in an HIV-naïve individual?
Tested PBMC from single needle-stick health care workers for CMI to HIV env peptides


LA Pinto et al. ENV-specific cytotoxic T lymphocyte responses in HIV seronegative health care workers occupationally exposed to HIV-contaminated body fluids. *J Clin Invest.* 1995; 96; 867-76

**Conclusion:**
One needle stick is sufficient to induce HIV-specific T helper and CTL responses, some responses lasting for 12 months.

**Question:**
Would a single parenteral exposure protect against HIV infection?
Are there observations in the SIV/macaque model that resemble the human ESN findings?
Macaques inoculated with subinfectious doses of SIV appeared resistant to challenge with an infectious dose of SIV.

M Clerici et al. T-cell proliferation to subinfectious SIV correlates with lack of infection after challenge of macaques. AIDS. 1994; 8: 1391-5

Titration of SIV\text{mneCLE11S} from 0.001-to-100 AID on 3-28-1990

<table>
<thead>
<tr>
<th>IV exposed</th>
<th>IR challenge</th>
<th>Viral isolation/PCR (wks)</th>
<th>Pathology</th>
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<td>J90219</td>
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<td>10 AID</td>
<td>++ ++ ++ ++ ++ ++ NT AIDS</td>
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?/? = virus isolation/PCR signal

At 51wk after IR, test T cell responses to 9 SIV peptides, H3N2 FLU, PHA

<table>
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<tr>
<th>Maq#</th>
<th>Peptide response:</th>
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<tr>
<td>J90044</td>
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<tr>
<td>F90184</td>
<td>0/9</td>
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<tr>
<td>89143</td>
<td>6/9</td>
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</tbody>
</table>

Peptide response: 0/9 5/9 0/9 6/9
Categories of ESN cohorts

Repeated unprotected sexual HIV exposure
  Promiscuous sex
  Stable discordant couples

Repeated intravenous HIV exposure
  I.V. drug abusers

Limited number of HIV exposures
  Hemophiliacs

Continuous HIV exposure
  Fetal/perinatal exposure

Single accidental HIV exposure
  Health care workers
  Laboratory workers
Using history to speculate...

“Moving forward” by glancing back....
Questions

Is the ESN phenomenon due to:
protective genetics?
activated immunity?
anti-viral mechanisms?
combinations of above?
Does the homozygous CCR5 32-bp (Δ32/Δ32) deletion account for the ESN phenomenon?

R Liu et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell.* 1996; 86: 367-77

Back to the maternal→fetal/perinate model of ESN,…

to consider an unexpected genetic effect, and possibly other complexities.
Could an ESN group be divided into subgroups with different infection risks?

![Graph showing infection risk comparison between two subgroups with a 10x difference.](image)
Would the 3% infected frequency be due to homozygosity for a resistance gene?
Mother-Child Class I HLA Concordance Increases Perinatal Human Immunodeficiency Virus Type 1 Transmission

Kelly S. MacDonald, Joanne Embree, Simon Njenga, Nico J. D. Nagelkerke, Irene Ngatia, Zeena Mohammed, Brian H. Barber, Jeckoniah Ndinya-Achola, Job Bwayo, and Francis A. Plummer

Mother-child class I HLA concordance and perinatal HIV-1 transmission.

MacDonald et al. J. Infect. Dis. 1998; 177: 551-556

Polycarpou et al. AIDS Res Hum Retrovir. 2002; 18: 741-6
In the MacDonald (Kenya) and Polycarpou (USA) cohorts, multiple mechanisms appear to contribute to resistance against vertical transmission:

One (affecting ~70% uninfected) appears to be independent of maternal/fetal HLA I matching.

The second (affecting remaining susceptibility) is regulated by maternal/fetal HLA-I concordance.
These findings suggest that MHC allorecognition is, in itself, an evolutionary driving force.
Do anti-viral and/or immunologic mechanisms contribute to the ESN phenomenon?
This single SIV/macaque experiment would need to be repeated (with controls) and expanded to verify the 1990-92 findings.

If confirmed, this result would suggest an inducible protective effect, because macaques are susceptible to AIDS.

This approach could open mechanistic analyses studies not possible in humans.
In contrast to long-term non-progressors (LTNP) and elite controllers (EC), ESN have passed the first test by resisting infection.

Have these potentially-relevant cohorts been overlooked in the search for AIDS vaccines?
ESN was a major reason for suggesting that CMI contributes to protection against HIV infection.

A Th1/Th2 switch is a critical step in the etiology of HIV infection. M Cleici, GM Shearer. *Immunology today*. 1993; 143; 107-11.

The Th1/Th2 hypothesis of HIV infection: new insights. M Clerici, GM Shearer. *Immunology today*. 1994;45; 575-81
At least 3 factors contribute to failure of CMI to protect against HIV infection

- HIV rapidly invades mucosal immunologic tissue.

- HIV rapidly activates multiple mechanisms of immune dysregulation and CD4 T cell depletion.

- HIV can rapidly mutate away from CTL epitopes used in AIDS vaccines.
Would solving the ESN mystery be useful in developing an effective AIDS vaccine?

Depends on whether the ESN phenomenon includes inducible(?) immunologic and/or anti-viral mechanisms, and whether these can be identified and elucidated.
Suggestion

Specific experiments should be developed:

1] to establish whether the ESN effect has inducible components,.....
   and if it does,
2] to determine their mechanisms of activation and protection.
As would be demonstrate in the 21st century....

Noninfectious interactions between HIV and CD4+ cells can result in immunopathogenesis. Herbeuval & Shearer. *Clin Immunol*. 2007

So,.. could noninfectious interactions between HIV and CD4+ cells also result in immune protection against HIV infection?
Protective immunity against HIV infection: has nature done the experiment for us?

Shearer & Clerici. *Immunol today*. 1996
APOBEC3G?

- Soros et al. PLoS Pathology 2007
- Rugeles et al. AIDS 2003

- MacDonald et al. J Infect Dis. 1998