Semen-mediated enhancement of HIV infection markedly impairs the antiviral efficacy of microbicides

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Semen Enhances HIV Infection

- Uninfected
- 0% Semen
- 0.4% Semen
- 2% Semen
- 10% Semen
- 50% Semen
SEVI
Semen-derived Enhancer of Viral Infection

Semenogelin-derived fibrils: A second set of semen amyloids

Endogenous Amyloids Consist of SEVI Fibrils

Usmani et al, Nature Communications, 2014
Endogenous Semen Amyloids Consist of SEM Amyloids

Endogenous Amyloids Are Ubiquitous in Semen

Proteostat

pFTAA

ThT

Usmani et al, Nature Communications, 2014
Endogenous amyloid bind HIV

Usmani et al, Nature Communications, 2014
Semen Samples from Patients with Ejaculatory Duct Obstruction Are Deficient in Enhancing HIV Infection

RLU/s-Background ($\times 10^3$)

Semen Pretreatment Concentration
- 50%
- 10%
- 2%
- 0.4%
- 0%

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<tbody>
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<td>Pooled Normal Semen</td>
<td>EDO Patients</td>
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Semen enhances HIV infection and harbors HIV-binding amyloids

How does this ability of semen to enhance HIV infection affect microbicide activity?
HIV microbicide candidates

• Anionic polymers (generally harmful)
  – Cellulose sulfate
  – Polystyrene acid
  – Polynaphthalene sulfonate
  – SPL7013 dendrimer

• Neutralizing antibodies
  – 2F5 (targeting gp41)
  – 2G12 (targeting gp120)

• Reverse Transcriptase inhibitors
  – NRTI (tenofovir)
  – NNRTI (nevirapine)

• Integrase inhibitor (Elvitegravir)
• Protease inhibitor (Indinavir)
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The HIV-enhancing Activity of Semen Impairs the Antiviral Efficacy of NRTIs and NNRTIs

Tenofovir

Zirafi et al, Science Translational Medicine, in press
The HIV-enhancing Activity of Semen Impairs the Antiviral Efficacy of NRTIs and NNRTIs

Zirafi et al, Science Translational Medicine, in press
The HIV-enhancing Activity of Semen Impairs the Antiviral Efficacy of Integrase and Protease Inhibitors

Zirafi et al, Science Translational Medicine, in press
The HIV-enhancing Activity of Semen Impairs the Antiviral Efficacy of Entry Inhibitors

**SPL7013**
- Polystyrene Acid: IC\textsubscript{50} (µg/ml)
  - 0.5ng: 21x
  - 0.05ng: ns
  - 0.05ng: ns

**2F5**
- Polynaphthalene Sulfonate: IC\textsubscript{50} (µg/ml)
  - 0.5ng: 9x
  - 0.05ng: 8x

**2G12**
- Cellulose Sulfate: IC\textsubscript{50} (µg/ml)
  - 0.5ng: 9x
  - 0.05ng: 8x

*Zirafi et al, Science Translational Medicine, in press*
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Semen Lacking HIV-enhancing Activity Lacks Ability to Counteract Antiviral Activity of HIV-targeting Microbicides

Zirafi et al, Science Translational Medicine, in press
Microbicides That Target Both HIV and Host-derived Viral Enhancement Factors
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• Maraviroc (targets host component CCR5)
The HIV-enhancing Activity of Semen Does Not Markedly Impair the Activity of Maraviroc

Note: Maraviroc targets host rather than viral component

Zirafi et al, Science Translational Medicine, in press
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