Is HIV becoming more virulent?

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Kenya Association of Physicians Symposium
19th September 2009
Introduction

• HIV is a recent human pathogen
• Speculated to have come from chimps 80 yrs
• Virus still adapting to human beings
• Therefore HIV may be becoming more or less virulent
  ▪ Different types of virus may induce different rates of disease progression
    Beaten JM, Chohan B, Lavreys L, Jaoko W et al. (2007)
    HIV-1 subtype D infection is associated with faster disease progression than subtype A in spite of similar plasma HIV-1 load
    Journal of Infectious Disease; 195:1170-80
  ▪ Switch of virus to strains that use CXCR4 coreceptors tend to appear at some point during infection in many people and this is associated with increased CD4 depletion & accelerate disease progression
    Troyer RM, Collins KR, Abraha A et al. (2005)
    Changes in human immunodeficiency virus type 1 fitness and genetic diversity during disease progression
    Journal of Virology; 79: 9006-18
Introduction

- Possible explanation for increased viral virulence
  - Adaptation to host resulting in poor cytotoxic T lymphocyte response, which are responsible for killing the virus in early infection, and therefore leading to early CD4 cell depletion
  - HAART drug pressure – killing the non-fit and selecting the more fit virus, more robust, more aggressive. Transmitted to others

- Measure of HIV epidemic does not take into account viral virulence
- Information on increase or decrease in viral virulence would give better indication as to success of control efforts
- Information on increase or decrease in viral virulence may be useful in guiding HIV vaccine research and development
Measurement of viral virulent

- Biological
  - HIV replicative capacity
      Survey of the temporal changes in HIV-1 replicative fitness in the Amsterdam cohort. *Virology*; **364**: 140-6

    Replicative fitness of historical and recent HIV-1 isolates suggests HIV-1 attenuation over time. *AIDS*; **19**: 1555–1564

*Replicative capacity is easy to measure for individual virus isolates but its relationship to pathogenic effects has been shown to be quite complex*

- Clinical measurement – Proxies for virulence
  - CD4 cell count at seroconversion
  - CD4 decline rate
  - Rise in viral set point
CD4 cell count at seroconversion

  - Cohort of military recruits in US arm
  - HIV negative prior to enrolment
  - HIV screening every 1-5 yrs
  - Initial CD4 cell counts among HIV seroconverters
  - Diagnosis by ELISA, confirmed by Western blot
  - 2174 participants
  - Mean age 27(± 7) yrs
  - 96% men
  - 44% white, 45% African American, 11% others
CD4 cell count at seroconversion

- Mean initial CD4 cell counts (cells/mm) fell with time

- In multiple regression models controlling for race, age, initial VL
  - CD4 cell count 1991-1995 < 1985-1990 by 79 cells/mm (p<0.001)
  - CD4 cell count 1996-2001 < 1985-1990 by 140 cells/mm (p<0.001)
  - CD4 cell count 2002-2007 < 1985-1990 by 118 cells/mm (p<0.001)
  - No difference in CD4 cell counts 1996-2001 and 2002-2007

- % of seroconverters with initial CD4 cell count < 200 cell/mm

- % of seroconverters with initial CD4 cell count <350 cells/mm
Figure 1. Adjusted mean initial CD4 cell counts, by race and time period.
CD4 cell decline rate & HIV viral set point

  Increasing clinical virulence in two decades of the Italian HIV epidemic. *PLOS Pathogens; 5*(5): e1000454
  - Patients attending a clinic in Italy
  - Infection acquired 1984 - 2005
  - 1423 patients
  - All Caucasian (white)
  - Median age at entry 28.9 yrs
  - 31.9% women
  - Exposure categories: IDU (46.3%), heterosexual (36.6%), MSM (17.1%)
  - Median number of CD4 cell counts used to measure decline = 9
  - Median baseline CD4 cell count = 596 cells/mm
CD4 cell decline rate & HIV viral set point

- CD4 slope decline slope correlated with date of confirmed infection
  - Spearman’s rank correlation test: rho = -0.16, p<0.001

- Multivariate analysis done to account for potential confounders (gender, exposure category, age at HIV confirmation, baseline CD4 cell count)
  - Date of confirmed infection associated with CD4 cell count decline: -2 cells/ul/year (95% CI: -2.7 to -1.3 cells/ul/yr)
  - CD4 cell count decline: heterosexuals & MSMs > IDUs

- Mean viral set point increase correlated with date of confirmed infection
A

Mean CD4 slope (cells/µL/year)

Mean date of confirmed infection

B

Mean setpoint (log_{10} RNA copies/mL)

Mean date of confirmed infection
CD4 cell decline rate & HIV viral set point

  Stable virulence levels in the HIV epidemic of Switzerland over two decades. *AIDS*; 20: 889-894
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## CD4 cell decline rate & HIV viral set point

<table>
<thead>
<tr>
<th></th>
<th>Decline in CD4</th>
<th>Viral set point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial CD4 count</td>
<td>p = 0.000</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>Date of confirmation of infection</td>
<td>p = 0.442</td>
<td>p = 0.234</td>
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<tr>
<td>Age</td>
<td>p = 0.687</td>
<td>p = 0.892</td>
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<tr>
<td>Gender</td>
<td>p = 0.489</td>
<td>p = 0.937</td>
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<tr>
<td>Route of infection transmission</td>
<td>p = 0.683</td>
<td>p = 0.770</td>
</tr>
</tbody>
</table>
Fig. 1
Limitation of studies on HIV virulence

- CD4 cell counts can fluctuate markedly during acute infection
- Clinical virulence combines effects of both host & virus factors and must be interpreted with caution
- “Empirical” measures of virulence are therefore not direct evidence for virus evolution

Conclusion

- There is no clear evidence off HIV becoming more virulent with time
- Where apparent HIV virulence has been observed, there are differences among exposure categories i.e. sub epidemics within same country
THANK YOU