Management of Severe Primary HIV Infection

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Outline

• What is severe PHI?
• How frequent is severe PHI?
• Is this occurring more frequently?
• Is severe PHI a poor prognostic indicator?
• Should ART be recommended?
• If so, what and for how long?
• Other aspects of management
Defining severe PHI

- **CD4**
  - CD4 < 200? Initial? After 3-6 months?

- **Viral load**
  - > 1 million? Initial? After 3-6 months?

- **Clinical**
  - Incubation?
  - Degree of symptomatology?
  - Duration?
  - Type: CNS?

CNS Involvement

- HIV penetrates the CNS very early after infection
- Increasing recognition of CNS disease
  - Sub-clinical cognitive impairment
  - Immune activation within the CNS
  - Variable CNS penetration of ART

- Numerous manifestations of CNS involvement described
- Anecdotal reports of “severe” CNS illnesses

- CNS involvement in PHI could serve as poor prognostic indicator
- CNS involvement in PHI could suggest future neurological disease
### Frequency of PHI symptoms and CNS Involvement

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Symptomatic</th>
<th>CNS</th>
<th>Other</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish males (n=86)</td>
<td>46 (53%)</td>
<td>Encephalitis 4 (5%)</td>
<td></td>
<td>Pedersen C et al; BMJ 1989</td>
</tr>
<tr>
<td>Swedish MSM (n=48)</td>
<td>19 (40%)</td>
<td>NS</td>
<td></td>
<td>Lindback S et al, BMJ 1994</td>
</tr>
<tr>
<td>US PHI cohort (n=74)</td>
<td>62 (84%)</td>
<td>NS</td>
<td>10 (14%) hospitalised</td>
<td>Schaker TW et al, Ann Intern Med 1998</td>
</tr>
<tr>
<td>QUEST PHI cohort (n=158)</td>
<td>142 (90%)</td>
<td>NS</td>
<td></td>
<td>Kinloch de Loes at al, JID 2005</td>
</tr>
<tr>
<td>Swiss and Australian PHI Cohort (n=259)</td>
<td>218 (84%)</td>
<td>3 (1%)</td>
<td></td>
<td>Vanhems P et al, CID 1998</td>
</tr>
<tr>
<td>Kenya FSW (n=218)</td>
<td>165 (74%)</td>
<td>NS</td>
<td></td>
<td>Luvreys L et al, CID 2006</td>
</tr>
<tr>
<td>SEROCO Italy (n=277)</td>
<td>135 (49%)</td>
<td>10 (3.6%)</td>
<td>13 (4.6%) other neuro</td>
<td>Boufassa F et al, JID 1995</td>
</tr>
<tr>
<td>CASCADE (n=5946)</td>
<td>1379 (23%)</td>
<td>48 (0.8%)</td>
<td>98 (1.6%) severe</td>
<td>Lodi S, personal communication</td>
</tr>
</tbody>
</table>

### Acute Fulminating Fatal Leukoencephalopathy As the Only Manifestation of Human Immunodeficiency Virus Infection

H. Royden Jones, Jr, MD,§ David D. Ho, MD,¶ Pierre Fogacs, MD,§ Lester S. Adelman, MD,* Mark L. Silverman, MD,¶¶ Richard A. Baker, MD,¶¶ and Patricia Locurto, MD*  

A case of acute human immunodeficiency virus (HIV) infection manifested by a rapidly fulminating, necrotizing, demyelinating encephalopathy that led to brain death in 5 days is reported. Autopsy demonstrated predominant white matter lesions, acute neuronal damage, and scanty cellular response. Cultures of cerebrospinal fluid were positive for HIV, suggesting an acute infection.

**Case Report**

**Fatal brain necrosis in primary HIV infection**

Wouter Meersman, Kristel Van Loethem, Katrien Legru, Guido Wilms, Iof Schuit, Marc Van Ranst, Anno

In November, 2004, a 31-year-old man was admitted to our hospital with a prominent morbilliform rash, pharyngitis, and a fever (40°C). He had been well until 2 weeks earlier, when he developed a fever, rash, and diarrhoea. HIV serology from 4 days earlier was negative. Neurological examination on admission was normal. However, 3 days later, he became lethargic and had a tonic-clonic seizure, necessitating intubation and

**Frequency of “Severe PHI” in CASCADE**

CASCADE 2006

Diagnosed in PHI

“Severe PHI”

- CD4 < 200 in 6 months
- Viral load > 1 million in 6 mo
- Seroconversion illness
- Severe illness

n=17146
n=5946
n=549 (9%)

242/4028 (6%)
255/2532 (10%)
1379/5946 (23%)
98/1379 (7%)

Lodi S, personal communication
Changing Frequency of severe PHI in CASCADE

Severe PHI occurs in a significant minority of patients at seroconversion

Lodi S, personal communication
### Clinical Severity of PHI and Prognosis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Features</th>
<th>Prognostic Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish males (n=86)</td>
<td>Duration of symptoms &gt; 14 days</td>
<td>AIDS or death</td>
<td>Pedersen C et al; BMJ 1989</td>
</tr>
<tr>
<td>Swedish MSM (n=48)</td>
<td>Presence of symptoms</td>
<td>CD4 &lt; 200, AIDS or death</td>
<td>Lindback S et al, BMJ 1994</td>
</tr>
<tr>
<td>Swiss and Australian PHI cohort (n=70)</td>
<td>Short Incubation period &lt; 21 days and symptoms &gt; 15 days</td>
<td>CD4 &lt; 200 or AIDS</td>
<td>Vanhems P et al; JID 2000</td>
</tr>
<tr>
<td>Swiss and Australian PHI Cohort (n=259)</td>
<td>Presence of symptoms and number of symptoms</td>
<td>Disease progression and death</td>
<td>Vanhems P et al, CID 1998</td>
</tr>
<tr>
<td>Kenya FSW (n=218)</td>
<td>Number of PHI symptoms</td>
<td>Death</td>
<td>Luvreys L et al, CID 2006</td>
</tr>
<tr>
<td>SEROCO Italy (n=277)</td>
<td>Presence of NS symptoms</td>
<td>AIDS</td>
<td>Boufassa F et al, JID 1995</td>
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</table>

### Influence of neurological involvement during PHI on HIV progression

- SEROCO cohort (Italy): n=277
- Frequency of neurological involvement
- Impact on HIV progression including subsequent NS disease

- 135 (49%) symptomatic; 23 (17% of symptomatic; 8% overall) had NS involvement
  - Lymphocytic meningitis (6%; 3%)
  - Acute encephalitis (1.5%; 0.7%)
  - Polyneuropathy (0.7%; 0.3%)
  - Peripheral mononeuropathy (9%; 4.4%)

- Faster disease progression if NS involvement
  - RR of AIDS 6.11 (p=0.005)
- No cases of CNS HIV disease in NS group
  - (commonest cause of death in others)

*Boufassa F et al, JID 1995*
Severe PHI is associated with a rapid disease progression

Theoretical benefit of ART in severe PHI

- To improve current clinical picture?
  - Symptoms
    - Spanish encephalitis series: spontaneous improvement with or without ART
      - Villar del Saz D et al; J Neurovirol 2008
  - Surrogate markers

- To alter natural history?
  - Short-term ART

- To prevent rapid progression?
  - ART
12 weeks ART in early HIV infection delayed the rate of CD4 decline

SMH n = 89 received 12 weeks of ART in early infection
CASCADE n = 179 not treated

Rate CD4 decline
SMH 51 cells/year
CASCADE 77 cells/year
P = 0.011


SPARTAC
n = 228
Excluded all those with a detectable plasma viral load at the time of stopping SCART

Randomisation

A Short course therapy SART
B Longer course therapy LART
C No therapy

3 monthly follow up

Time to CD4 count <350
ACTG 5217 (SETPOINT)

Recent HIV Infection

TDF/FTC/r/LPV
36 weeks

Observation only

Viral load at weeks 72-76
Disease progression
Adverse events

Study terminated after DSMB review August 2009
Two few viral load endpoints
But
Significantly greater disease progression in observation group
20/39 needed ART within 18 months

Viral load at weeks 72-76
Disease progression
Adverse events
**ACTG 5271 (SETPOINT)**

- **Inclusion criteria:**
  - CD4 of $\geq 350$
  - CD4% of $\geq 14$

- **Exclusion criteria:**
  - Category B or C HIV Disease

**PHI Severity and effect of transient ART**

- Higher baseline viral load - worse virological outcome after treatment interruption (QUEST)
  
  *Barqasho B et al, HIV Medicine 2009*

- Higher viral load and lower CD4 count – worse virological outcome after treatment interruption (ACTG 371)
  
  - CD4 < 200 excluded

  *Volberding P et al, AIDS 2009*

- Higher baseline viral load – worse virological outcome (SPARTAC)

  *Fidler et al, Boston Seroconverter Meeting, 2009*
Short-term ART may be beneficial for some

Less likely to be beneficial in severe PHI

Choice of ART

• Integrase?
  – reduce size of viral reservoir
  – rapid reduction in viral load

• CCR5 inhibitors?
  – good penetration to “sanctuary” sites
  – CNS virus is usually CCR5 tropic
  – effect on immune activation

• CNS penetration?
  – preferable if CNS disease

• NNRTIs?
  – risk of transmitted resistance
  – Pk and interruption
Other aspects of management

• Diagnosis

• Contact Tracing

• Impact on transmission

Missed Opportunities to detect primary HIV infection?

<table>
<thead>
<tr>
<th>Location</th>
<th>% symptomatic</th>
<th>% seen in HC</th>
<th>Diagnosis made</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>89%</td>
<td>88%</td>
<td>26% (10% of total)</td>
<td>15% hospitalised !</td>
</tr>
<tr>
<td>US</td>
<td>n/a</td>
<td>52%</td>
<td>17%</td>
<td>most seen &gt; 3 times</td>
</tr>
<tr>
<td>Brighton</td>
<td>71%</td>
<td>51%</td>
<td>56% (19% of total)</td>
<td>GP &gt;&gt; A&amp;E &gt; others</td>
</tr>
</tbody>
</table>

• Brighton study: almost all MSM with pharyngitis, fever, rash
• HCWs frequently not aware of sexuality

• Significance of PHI in driving onward transmission
  • infectiousness
  • sexual behaviour

Testing for HIV: concise guidance

Adrian Patlizeanu, Martin Fisher and Ed Ong on behalf of the HIV Testing Guidelines Writing Committee

Abstract - HIV is a substantial public health problem as the majority of those living with the virus remain fit and well on treatment. Despite this, a significant number of people in the UK are unaware of their HIV infection and remain at risk.

While the availability of highly active anti-retroviral therapy (HAART) has transformed the outcome for individuals with HIV, many are left living with the disease. Early detection is therefore crucial. This paper provides guidelines for the testing of individuals at risk for HIV.

Suspected primary HIV infection

Primary HIV infection (PHI) or seroconversion illness occurs in approximately 60 per cent of individuals, typically two to four weeks after infection. It is well recognised that this represents an unique opportunity to prevent onward transmission as an individual is considerably more infectious at this stage. Furthermore, this may be the only clinical opportunity to detect PHI before advanced immunosuppression many years later.

It is known that the features of PHI are non-specific, that individuals usually do not present to medical services (primary or emergency care) but frequently the diagnosis is missed or not suspected. The typical symptoms include a combination of any of:

- fever
- rash (maculopapular)
- myalgias
- pharyngitis
- headache/aseptic meningitis
Informing at-risk communities about PHI

- Seattle: HIV-negative MSM attending STD clinic, 2004-2005; Questionnaire about knowledge of PHI symptoms
  - 96/150 (64%) named >/= 1 symptom
  - 18/46 (39%) knew could resemble flu and would seek medical attention
  - 15/23 (65%) had sought medical attention with week-long flu symptoms in previous year
    - 7 (30%) were tested for HIV

Stekler JS et al, JAIDS 2006

Contact tracing in PHI versus chronic infection

- North Carolina, 2002-2007
  - pooled RNA testing
  - 3rd generation antibody testing
  - Acute HIV (AHI) if: +RNA –Ab, or –Ab within 30 days; otherwise established HIV (EHI)
    - EHI n=9044; AHI n=120
  - More newly identified infections from AHI:
    151/120 versus 4/9044 (p=0.03)
    RR 1.93 (1.06-3.53)

Moore ZS et al; JAIDS 2009

- Brighton – smaller numbers, similar findings
  - More "successful" contact tracing if PHI
  - Newly identified infections more likely to be also EHI

Roberts J et al; BHIVA 2006
Brighton phylogenetic study
Factors associated with transmission (Multivariable)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Load (per log_{10} increase)</td>
<td>1.68</td>
<td>1.19 - 2.36</td>
<td>0.003</td>
</tr>
<tr>
<td>Recent Infection</td>
<td>3.43</td>
<td>1.52 - 7.73</td>
<td>0.003</td>
</tr>
<tr>
<td>STI during interval</td>
<td>5.64</td>
<td>2.65 - 12.02</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (per 5 years older)</td>
<td>0.68</td>
<td>0.54 - 0.85</td>
<td>0.0009</td>
</tr>
<tr>
<td>On HAART</td>
<td>0.28</td>
<td>0.05 - 1.44</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Increased likelihood of transmission in PHI
2% of follow-up time but 24% of transmissions

Fisher, CROI 2009

Other psychosocial Issues

• Acceptance of diagnosis

• Immediate commencement of treatment

• Continuous treatment vs short-term
Managing the patient with severe PHI

Practical Approach?

Viral load
Type of virus

CD4 count
Immune response
Activation
Genetics

Virus

Patient

Clinical Picture

Symptomatology
Incubation, type of symptoms, duration
Treatment of Severe PHI

Who to treat?
• Clinical features
  – CNS involvement, severity of acute illness
• CD4 count
  – <200 at any stage
• Viral load
  – ? Not in isolation

When to treat?
• Early; dependent on clinical features

What to use?
• Consider resistance, pk and CNS penetration

For how long?
• Continuous if acceptable to patient
• If ART not acceptable, then close monitoring

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Acute Fulminating Fatal Leukoencephalopathy As the Only Manifestation of Human Immunodeficiency Virus Infection

- Make the diagnosis of HIV seroconversion
- Immediate antiretroviral therapy
- Anti-herpesvirus therapy
- Broad spectrum antibiotic (e.g. ceftriaxone)
- +/- corticosteroids

Silverman ML, Baker RA, Locurato P. Acute fulminating fatal leukoencephalopathy as the only manifestation of human immunodeficiency virus infection. Ann Neurol 1986;20:510–512

SWINE FLU

Do NOT come to the hospital if you have:
- Fever
- Headache
- Sore throat
- Muscle aches

NHS
Acknowledgements

• Sarah Fidler, Imperial College
• Julie Fox, Guy’s and St Thomas’
• Sara Lodi and Kholoud Porter, CASCADE
• Sabine Kinloch de Loes, Royal Free Hospital