Blood, Toil and Tears
Outcomes over 25 Years in People with Haemophilia and HIV

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Outlines

- Review clinical outcomes in Victorian people with haemophilia and HIV over the 25 years since first identified transmission of HIV
- Present outcomes in detail in those who remained alive in January 2006
- Discuss introduction of novel antiviral therapies such as enfuvirtide in this group
Background

- Introduction of highly-active antiretroviral therapy (HAART) and of therapies for HCV in recent years is likely to have altered both clinical outcomes and quality of life for patients with haemophilia and chronic viral infections.
- Little information on Australian population since advent of highly active antiretroviral therapy.
Aims

- Major clinical outcomes
  - Progression to AIDS-defining illness
  - Progression to ‘end-stage’ liver disease
  - Mortality stratified by cause

- Further clinical outcomes
  - Current virological and immunological status for HB, HCV, and HIV
  - Details of treatment and treatment response
Population

- All people with haemophilia treated at Victorian centres (e.g., Children’s Hospital, the Alfred) who were diagnosed with HIV
- All HIV infected people were also found to be HCV infected
- 90 patients
- Excluded 3 who were not originally treated or diagnosed in Victoria, and who have subsequently left the state
- Follow-up available for all people (limited in 2 who have left the state)
Population

- Baseline characteristics
  - Male 89 (98%)
  - Haemophilia type:
    - A 90% (81 patients)
    - B 8% (7)
    - VWD 2.2% (2)
  - Haemophilia Severity:
    - Severe 76%, Moderate 20%, Mild 4%
### Mortality

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>29</td>
<td>56%</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>9</td>
<td>17%</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>27%</td>
</tr>
<tr>
<td>(Bleeding)</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>(Suicide)</td>
<td>2</td>
<td>4%</td>
</tr>
</tbody>
</table>

- 52 deaths (57%), leaving 38 (43%) who remain alive
Mortality

Columns show number of deaths for each two-year period 1984–2006 (scale on left axis). Curve shows cumulative deaths as percentage of total for each cause (scale on right axis).
Mortality

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Curve shows cumulative death as percentage of total for each cause (scale on right axis).
Mortality

Columns show number of deaths for each two-year period 1984-2000 (scale on left side). Curve shows cumulative death as percentage of total for each cause (scale on right side).
Progression

- Collected across entire cohort, including patients who subsequently died of any cause
- AIDS-defining illnesses
  - 36 with AIDS-defining illness, of whom 28 subsequently died
  - Of those 28 deaths, 25 directly attributable to AIDS
  - PCP, cryptococcosis, and candidiasis major AIDS defining illnesses
  - PCP, cryptococcosis and malignancy major AIDS related causes of death
Progression

- End-stage liver disease
  - Attributed on basis of Child’s score or development of defined complications
  - 9 developed end-stage liver disease, of whom 2 remained
  - 3 deaths without clear viral identification, attributed to “non B hepatitis”
Progression
Progression
Survivors: Psychosocial Outcomes

- Employment: 22 Yes, 14 No
- Partnership: 21 Yes, 15 No
- Offspring: 13 Yes, 23 No
- Bereavement: 7 Yes, 29 No
Survivors: Clinical Outcomes

- **HIV**
  - **Treatment**
    - Number on HAART: 33 (85%)
    - Median HAART line: 4 (range 0 to 10)
    - One patient remains on single-agent ART (last viral load 600 with CD4 count 310)
  - **Virological control**
    - Median HIV viral load: <50 copies/mL (range <50->1000)
Survivors: Clinical Outcomes

- Immunological control
  - Median current CD4 count: 429 cells/µL (range 23 to 996)
  - Median CD4 nadir: 113 cells/µL (range 1 to 400)

- Progression and complications
  - Number with AIDS defining illness: 8 (21%)
    - 3 with candidiasis; 2 with PCP; 1 each with MAC, cerebral toxoplasmosis, cryptococcosis
Survivors: Clinical Outcomes

- **HCV**
  - Genotype available in 23
    - A 58% (14), B 7 (30%), C 1 (4%), D 1 (4%)
  - Treatment
    - 8 treated, all with pegylated IFN and ribavarin
    - 3 assessable for SVR: none achieved
Virological control

- Median HCV viral load: $8 \times 10^5$ copies/mL (range <615 to 2000)

Progression

- 2 with end-stage complications (Child’s score B or C)

HBV

- All have evidence of past infection with HBV
- 8 with chronic infection, all with undetectable viral loads at analysis
Therapeutic Challenges

- Long duration of HIV infection
- Antiretroviral drug resistance following sequential monodual HIV antiretroviral therapy prior to the advent of highly active antiretroviral therapy (HAART)
- Chronic liver disease associated with high rates of coinfection with Hepatitis C and/or Hepatitis B
- Unique susceptibility to certain toxicities, notably bleeding
Arrival of new classes of antiretroviral agents offers the prospect of improving further improving outcomes for people living with HIV

Particular challenges in people with haemophilia and HIV

- Reduce therapeutic choices, as concerns regarding tolerance of lead clinicians to avoid novel agents in this patient group despite possible benefits
- Limit clinical outcomes of this group
Enfuvirtide (T20)

- First of a new class of antiretrovirals, the viral entry inhibitor
- Acts by preventing gp41-mediated fusion of the viral envelope with the target cell membrane
- Effective in combination with optimised background antiretroviral therapy
- Shows no cross-resistance with existing antiretroviral agents
Patient Characteristics

- All male, age range 27 to 51, all with severe haemophilia
- Variable bleeding frequency; two on prophylaxis
- Three with poor viral control secondary to resistance across multiple viral classes
  - Median four lines therapy
  - Viral loads 39,000 copies/ml to >100,000 copies/ml
  - CD4 counts 135 to 162 cells/µL
- One with control related to poor oral absorption of antiviral
Introduction of Enfuvirtide

- Enfuvirtide introduced with ‘background’ optimised HAART.
- Each patient received targeted education in use.
  - Direct demonstration of injection technique including injection rotation and meticulous technique.
  - Audiovisual education aids.
- Regular monitoring for adverse events, including change in pattern of bleeding complications, following introduction.
Enfuvirtide Efficacy

Viral Load (Copies/μL)

Time (months) from commencement of enfuvirtide

*Six months follow-up available
UD: Undetectable (<50 Copies/μL)
Enfuvirtide Efficacy
Enfuvirtide Tolerability

- Local skin reactions at injection site commonly reported.
- No patient experienced significant local bleeding at the injection site.
- No increase in the rate or severity of systemic bleeding was apparent, even in those patients with high rates of bleeding and those not receiving prophylactic coagulation factors.
- Three patients remain on enfuvirtide-containing regimens.
Conclusions

- These data confirm the profound impact of HIV infection on the longevity and lives of many people with haemophilia.

- The remarkable outcomes of antiviral therapy, particularly HAART, can be seen in reduction in mortality and progression and in the achievement of life goals.

- The impact of HCV infection remains to be determined.

- Novel therapies can deliver considerable clinical benefit if carefully introduced and monitored.
Acknowledgments

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