Surrogate Endpoints
Example from HIV:
From Clinical Endpoints
to Viral Load

Marc Cavaillé-Coll, M.D., Ph.D.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
marc.cavaillecoll@fda.hhs.gov
Disclaimer

• The opinions and conclusions expressed in this presentation are those of the presenter and should not be interpreted as those of the FDA.
• I have no conflicts.
• Slides courtesy of Dr. Jeffery S. Murray from the Division of Antiviral Products
Clinical Endpoints

• AIDS-defining opportunistic infections (OI) and other conditions
  – Infections: viral, fungal, bacterial, parasitic, mycobacterial
  – Syndromes (wasting),
  – Malignancies

• Standard definitions established
• Usually first occurrence counted
• Events weighted equally, even if occur at different levels of immune function deficiency
Clinical Endpoints and Associated Peripheral Blood CD4+ Cell Count per µL

200

Tuberculosis
Recurrence Pneumonia
Kaposi Sarcoma
Esophageal Candidiasis

100

Pneumocystis
Toxoplasmosis
Cryptococcus
Wasting

50

CMV retinitis
PML
MAC
Lymphoma
Evolution of Surrogate Endpoints for HIV Drug Approval

1991
CD4 p24 Antigen

1996
CD4 HIV-RNA

3TC, SQV

1996
HIV-RNA CD4

RTV, IDV, NFV, NVP

Current
HIV-RNA

Numerous drugs

ZDV

ddI, ddC, d4T

Numerous drugs
Background: HIV-RNA (viral load)

- HIV Viral Load uses in 1996
  - Several assays available
    - lower limit of quantification 50-80 copies
  - Significant change (2 s.d.) = 3-fold or 0.5 log change
  - Prognostic indicator of disease progression, precedes CD4 cell decreases (CD4 better marker of net degree of immunosppression and criteria for starting treatment).
  - Used for assessing response to therapy
  - Viral rebound associated with drug resistance, signifies need to change regimen
Collaboration

• 1996 Surrogate Marker Working Group
  – Industry, academia, and government

• Sponsors, FDA, NIH analyzed data to assess:
  – Correlations between viral load and clinical outcome
  – Correlations between short-term viral load suppression and durability of viral load response

• July 1997 Antiviral Advisory Committee
  – Meta-analysis presented
# HIV RNA and Clinical Benefit

5 Analyses (1996), >5000 patients

<table>
<thead>
<tr>
<th>ANALYSES</th>
<th>N</th>
<th>REGIMENS</th>
<th>CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Abbott</td>
<td>159</td>
<td>PI + NRTIS</td>
<td>21</td>
</tr>
<tr>
<td>Single Study (subset)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) NIH AIDS Clinical Trial Group</td>
<td>1000</td>
<td>Many</td>
<td>218</td>
</tr>
<tr>
<td>Multiple Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Glaxo-Wellcome Studies</td>
<td>1581</td>
<td>ZDV +3TC (others)</td>
<td>209</td>
</tr>
<tr>
<td>Multiple Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) Pharmacia &amp; Upjohn Studies:</td>
<td>1842</td>
<td>DLV+ZDV, DLV+DDI</td>
<td>230</td>
</tr>
<tr>
<td>Two Studies</td>
<td></td>
<td>ZDV, DDI</td>
<td></td>
</tr>
<tr>
<td>5) Roche Study</td>
<td>940</td>
<td>SQV+DDC, SQV, DDC</td>
<td>170</td>
</tr>
<tr>
<td>Single Study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Association of Viral Load Reduction and Clinical Benefit (3 slides)

- Magnitude of Reduction
- Nadir of Reduction
- Duration of Reduction
Clinical Progression vs. HIV RNA Reduction

POOLED ACTG STUDIES

ADJ. RR (natural log)

WEEK 24 HIV RNA Reduction

Stratifying factors
- study and treatment
- none
- study
- treatment

>1.0 log
0.5-1.0 log
0-0.5 log
no reduction
Progression vs. Viral Load Nadir

GSK Analyses

Viral Load Nadir (copies/mL)

Incidence

<Median

>Median

<400 <500 <20,000 >20,000

Viral Load Nadir (copies/mL)
### Clinical Hazard by Duration of Reduction

**Pharmacia-Upjohn Analyses**

<table>
<thead>
<tr>
<th>Response Duration</th>
<th>Hazard ratio</th>
<th>95% CI for HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>#DAYS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>1-29</td>
<td>0.68</td>
<td>(0.43, 1.04)</td>
</tr>
<tr>
<td>30-57</td>
<td>0.72</td>
<td>(0.41, 1.27)</td>
</tr>
<tr>
<td>58-113</td>
<td>0.55</td>
<td>(0.32, 0.95)</td>
</tr>
<tr>
<td>114-141</td>
<td>0.26</td>
<td>(0.128, 0.528)</td>
</tr>
<tr>
<td>&gt;142</td>
<td>0.29</td>
<td>(0.145, 0.564)</td>
</tr>
</tbody>
</table>
Analyses: Summary of Findings

• There is lower risk of clinical progression associated with
  – HIV RNA decreases (> 0.5 log)
  – Greater reductions in HIV RNA
  – More sustained reductions (> 8-12 weeks)

• Suppression of HIV-RNA below assay quantification is associated with
  – longer duration of virologic suppression
  – less emergence of HIV resistance
July 1997 AC Meeting: Conclusions

- HIV RNA is a suitable endpoint for:
  - Accelerated Approval (24 weeks) AND...
  - Traditional Approval (48 Weeks)
- Concordance with other markers (CD4)
- Precedents for “Lab” Endpoints:
  - Cholesterol and drugs for D.M.
Conclusions

• Validated surrogate endpoints can substantially facilitate drug development

• Multiple trials, large databases, and other types of supporting data are needed to “validate” a surrogate

• 100% correlation of a surrogate and clinical endpoint is not likely. Clinical Endpoints are not perfect gold standards

• There is room for improvement in enrolling and treating greater numbers of transplant patients under clinical protocols where these data can be collected
Selected References
