Introduction to Studies on the Toxicology of AIDS Therapeutics

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Disclaimer

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Studies on the Toxicology of AIDS Therapeutics

- Acquired Immune Deficiency Syndrome (AIDS) is a viral-based disease that is mediated by human immunodeficiency virus type 1 (HIV) infection.

- Many anti-retroviral therapies have been developed to treat the disease; successful perinatal treatment to avoid mother-to-child transmission.

- AZT is a nucleoside analogue that inhibits reverse transcriptase and reduces transmission of the disease. Other anti-HIV compounds include NVP, 3TC, EFV and NFV.

- With reports on the potential mutagenicity and/or carcinogenicity of nucleoside analogues, studies were designed to test the mutagenicity and carcinogenicity in rodents as predictors of possible human disease outcome.
2-Year Bioassays of AIDS Therapeutics

*Industry sponsored 2-year bioassay with AZT*

*NIH studies*
**CD-1 mice**
- Olivero et al. 1997
- Diwan et al. 1999

**B6C3F1 mice and F344 rats**
- Walker et al. 2007
2-Year Bioassays of AIDS Therapeutics

Industry sponsored 2-year bioassays
- Ayers et al., 1996
  - CD-1 mice (daily gavage, up to 120 mg/kg/da, AZT >90 days reduced); increased incidence of vaginal squamous cell carcinoma.
  - CD rats (daily gavage, up to 600 mg/kg/da AZT, >90 days reduced) equivocal increase in vaginal squamous cell carcinoma.

NIH studies
- Ayers et al., 1997
  - Female CD-1 mice (intravaginal, 2x daily up to 4 mg AZT); increase incidence in vaginal squamous cell carcinoma.
  - Pregnant CD-1 mice (GD10 up to 24 months, up to 40 mg/kg/da AZT); increased incidence in vaginal squamous cell carcinoma in 2 highest dose groups.
2-Year Bioassays of AIDS Therapeutics


NIH studies

- Pregnant CD-1 mice (GD12-18, up to 450 mg/kg/da AZT); at 1 yr, increased incidence of lung, liver, skin and female reproductive tract tumors; at 2 yr, increased incidences of lung, mammary gland, and ovarian tumors and histiocytic sarcomas (female F₁) and seminal vessicle tumors (male F₁).

- Female C57/Bl6 (X C3H male) (GD12-18, up to 480 mg/kg/da with AZT); at 2 yrs, increase in hepatic carcinoma and hemangiosarcoma in F₁ males.

- Female F344 rats (GD15-21, up to 480 mg/kg/da AZT); at 2 yrs, increased incidence of mononuclear cell leukemia in F₁ females.

Olivero et al., 1997; Diwan et al., 1999

Olivero et al., 1997; Diwan et al., 1999

Walker et al., 2007

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2-Year Bioassays of AIDS Therapeutics (NIEHS/NTP)

- 2-Year Bioassay in B6C3F1 mice, life-time exposure to AZT
  *NTP TR 469*

- 2-Year Bioassay in Swiss mice, transplacental exposure to AZT
  *NTP TR 522*
2-Year Bioassays of AIDS Therapeutics (NIEHS/NTP)

NTP TR 469 (life-time exposure)
- B6C3F1 mice (gavage up to 120 mg/kg/da AZT)
- Clear evidence of carcinogenic activity in female mice (vaginal squamous cell neoplasms)
- Equivocal evidence of carcinogenic activity in male mice (Harderian gland, renal tubule neoplasms)
2-year Bioassays of AIDS Therapeutics (NIEHS/NTP)

2-Year Bioassay in B6C3F1 mice, life-time exposure to AZT
*NTP TR 469*

2-Year Bioassay in Swiss mice, transplacental exposure to AZT
*NTP TR 522*

- *NTP TR 522 (transplacental exposure)*
  - CD-1 mice (gavage up to 300 mg/kg/da AZT)
  - Clear evidence of carcinogenicity in male mice (alveolar/bronchiolar neoplasms)
  - No evidence of carcinogenic activity in female mice.
AZT, Zidovudine  
3TC, Lamivudine  
EFV, Efavirenz  
NVP, Nevirapine  
NFV, Nelfinavir
2-Year Bioassays of AIDS Therapeutics (FDA/NCTR)

- 2-Year Bioassay of AZT, 3TC, NVP following transplacental exposure
  *NTP TR 569*

- 2-Year Bioassay of AZT, 3TC, NVP, NFV, EFV following transplacental/perinatal exposure
  *(to be reviewed in 2013)*

- Bioassay of AZT in Transgenic mice following transplacental/perinatal exposure
  *GMM 14*

- Bioassay of AZT, 3TC, NVP in p53 +/- Transgenic mice following transplacental/perinatal exposure
  *GMM 16*
NTP TR 569 (transplacental exposure study; GD12-18, C57/Bl6N female, x C3H male)

- AZT: no evidence of carcinogenic activity in male B6C3F1 mice; equivocal evidence in female mice [thyroid gland neoplasms (primarily adenoma) and subcutaneous skin fibrosarcoma or sarcoma].

- AZT and 3TC: no evidence of carcinogenic activity in male B6C3F1 mice; equivocal evidence in female mice [lung alveolar/bronchiolar adenomas].

- AZT, 3TC and NVP: some evidence in male mice [subcutaneous skin neoplasms (fibroma, fibrous histiocytoma, fibrosarcoma)]; equivocal evidence in female mice [subcutaneous skin fibrosarcoma].

- AZT, 3TC and NFV: no evidence in male or female mice.
2-Year Bioassays of AIDS Therapeutics (FDA/NCTR)

**Transplacental/perinatal exposure study**
Maternal exposure (GD 12-21; C57/Bl6N female x C3H male) and F₁ neonatal exposure (PND1-8), monitor for up to 2 yrs
- AZT, AZT/3TC, AZT/3TC/NVP, AZT/3TC/NFV, AZT/3TC/EFV
- to be reported in 2013

Bioassay of AZT in
Transgenic mice following transplacental/perinatal exposure
GMM 14

Bioassay of AZT, 3TC, NVP following transplacental/perinatal exposure
GMM 16

Bioassay of AZT, 3TC, NVP following transplacental/perinatal exposure (to be reviewed in 2013)
2-Year Bioassays of AIDS Therapeutics (NCTR)

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These two reports reviewed at NTP Technical Report review panel, 8-9 Feb 2012
## 2-Year Bioassays of AZT - MICE

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MOUSE</th>
<th>DOSE (maximum)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayers et al., 1996</td>
<td>CD-1</td>
<td>Gavage; 120 mg/kg/d</td>
<td>Vaginal squamous cell carcinoma</td>
</tr>
<tr>
<td>Ayers et al., 1997</td>
<td>CD-1</td>
<td>Intravaginal; 8 mg/da</td>
<td>Vaginal squamous cell carcinoma</td>
</tr>
<tr>
<td>Ayers et al., 1997</td>
<td>CD-1</td>
<td>GD10-2 yr; 40 mg/kg/d</td>
<td>Vaginal squamous cell carcinoma</td>
</tr>
<tr>
<td>Oivero et al., 1997; Diwan et al., 1999</td>
<td>CD-1</td>
<td>GD12-18; 450 mg/kg/d</td>
<td>Lung, mammary, ovarian, histiosarcoma ♀, seminal vessicle ♂</td>
</tr>
<tr>
<td>Walker et al., 2007</td>
<td>C57/Bl6</td>
<td>GD12-18; 480 mg/kg/d</td>
<td>Hepatocellular carcinoma, hemangiosarcoma ♂</td>
</tr>
<tr>
<td>TR 469</td>
<td>B6C3F1</td>
<td>Gavage; 120 mg/kg/d</td>
<td>Vaginal squamous cell neoplasms</td>
</tr>
<tr>
<td>TR 522</td>
<td>CD-1</td>
<td>Transplacental; 300 mg/kg/da</td>
<td>Alveolar/bronchial neoplasms ♂</td>
</tr>
<tr>
<td>TR 569</td>
<td>B6C3F1</td>
<td>GD12-18; 240 mg/kg/d</td>
<td>Equivocal ♀; thyroid adenoma, subcutaneous fibrosarcoma</td>
</tr>
</tbody>
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