NTP
National Toxicology Program

Introduction to Studies on the Toxicology of AIDS Therapeutics

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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 Bioassaysof AIDS Therapeutics

Industry sponsored 2-year bioassay with AZT

- Ayers et al 1996, 1997

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 bioas

- Aye

NIH studies

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.

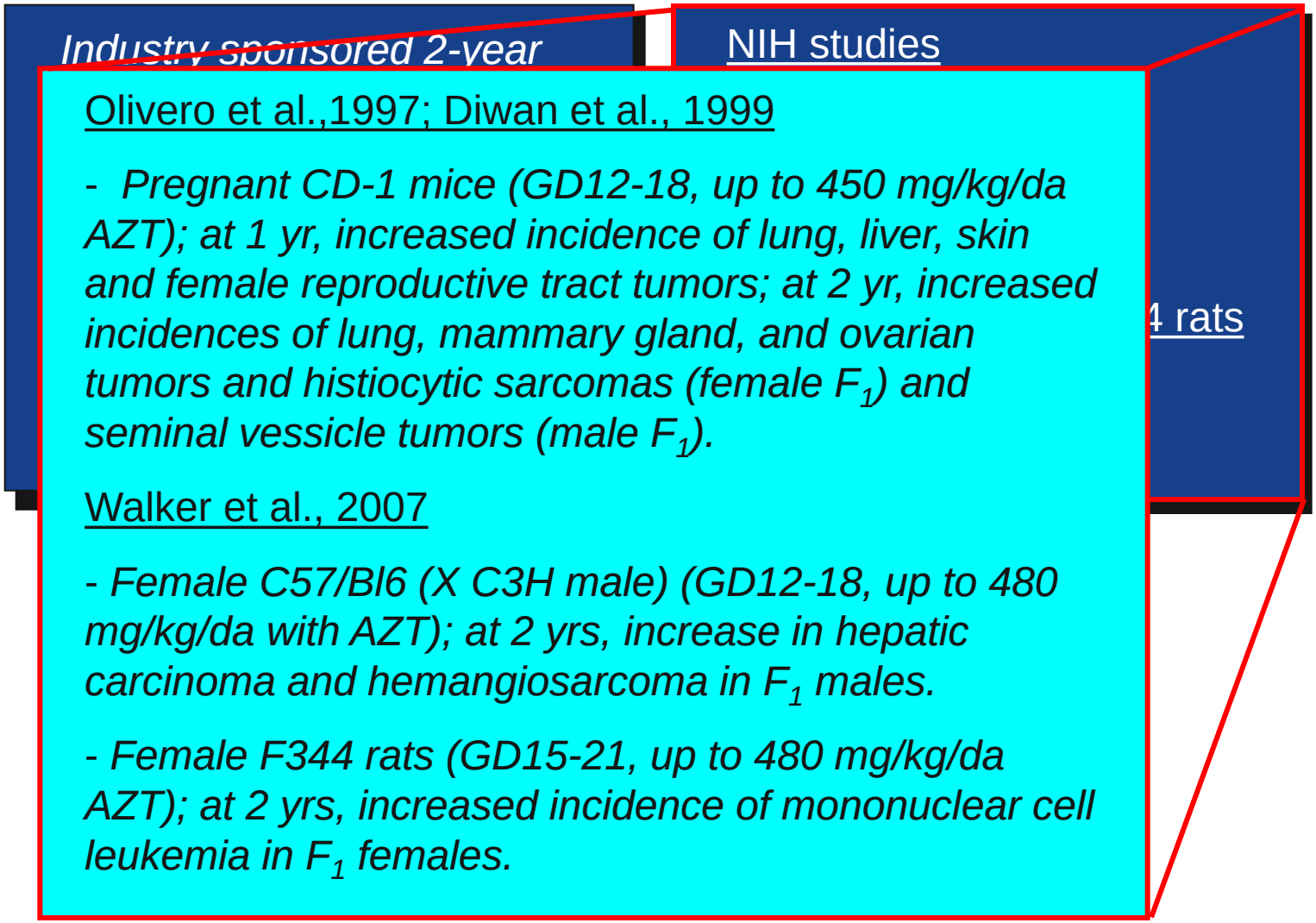
-CD rats (daily gavage, up to 600 mg/kg/da AZT, >90 days reduced) equivocal increase in vaginal squamous cell carcinoma.

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



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)

2-Year Bioassay in B6C3F1 mice, li
AZT
NTP TR

2-Year Bioassay in Swiss mice, transplacental

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 46

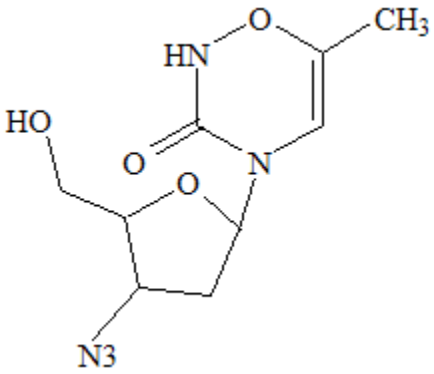
2-Year Bioassay in Swiss mice, transplacental

NTP TR 522 (transplacental exposure)

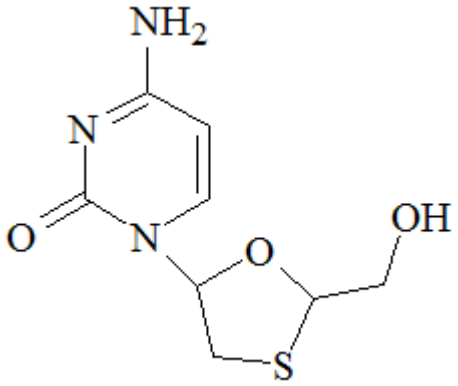
- *CD-1 mice (gavage up to 300 mg/kg/da AZT)*

- *Clear evidence of carcinogenicity in male mice (alveolar/bronchiolar neoplasms)*

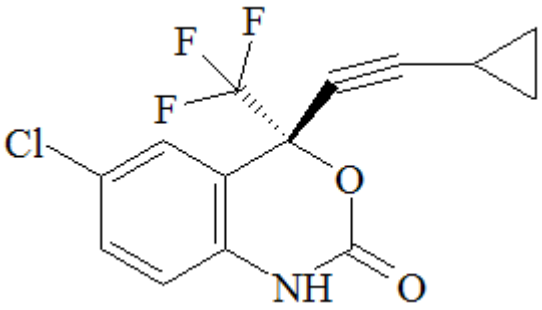
- *No evidence of carcinogenic activity in female mice.*



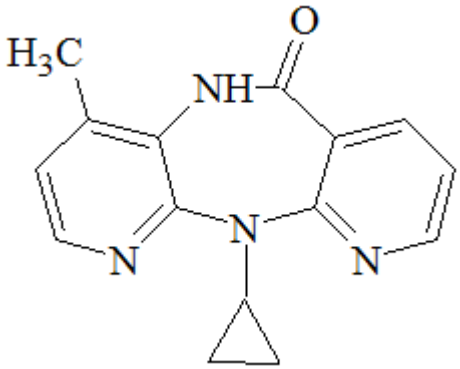
AZT, Zidovudine



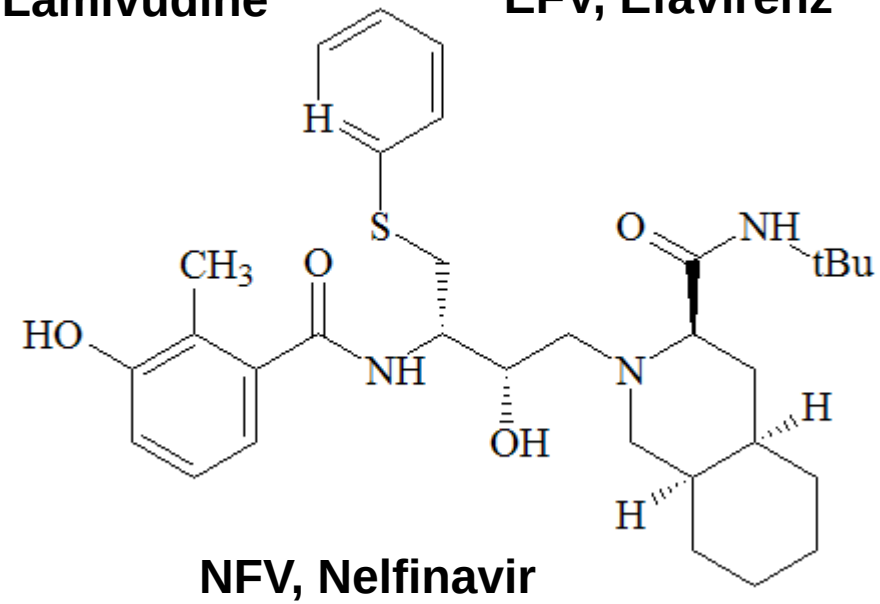
3TC, Lamivudine



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

2-Year Bioassays of AIDS Therapeutics (FDA/NCTR)

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 F_1 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

Transgenic mice following transplacental/perinatal exposure
GMM 14

in p53 +/- Transgenic mice following transplacental/perinatal exposure
GMM 16

2-Year Bioassays of AIDS Therapeutics (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

in 2013)

These two reports reviewed at NTP Technical Report review panel, 8-9 Feb 2012

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

2-Year Bioassays of AZT - MICE

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