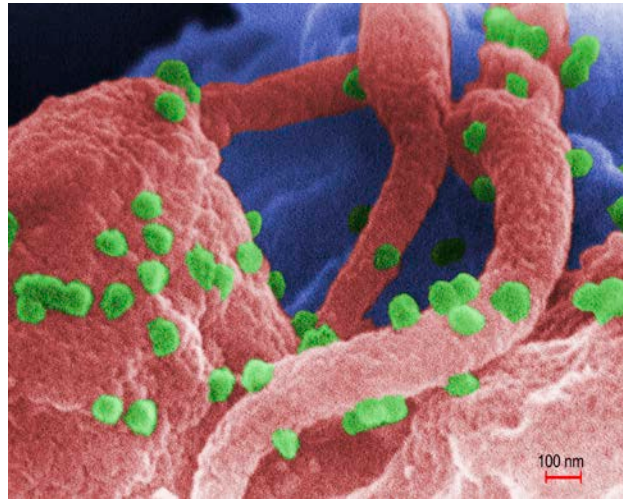


Draft RoC Monograph HIV-1 Virus



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NTP Peer Review Meeting
December 17, 2015



Outline

Properties and detection

Transmission

Exposure

Mechanisms of carcinogenesis

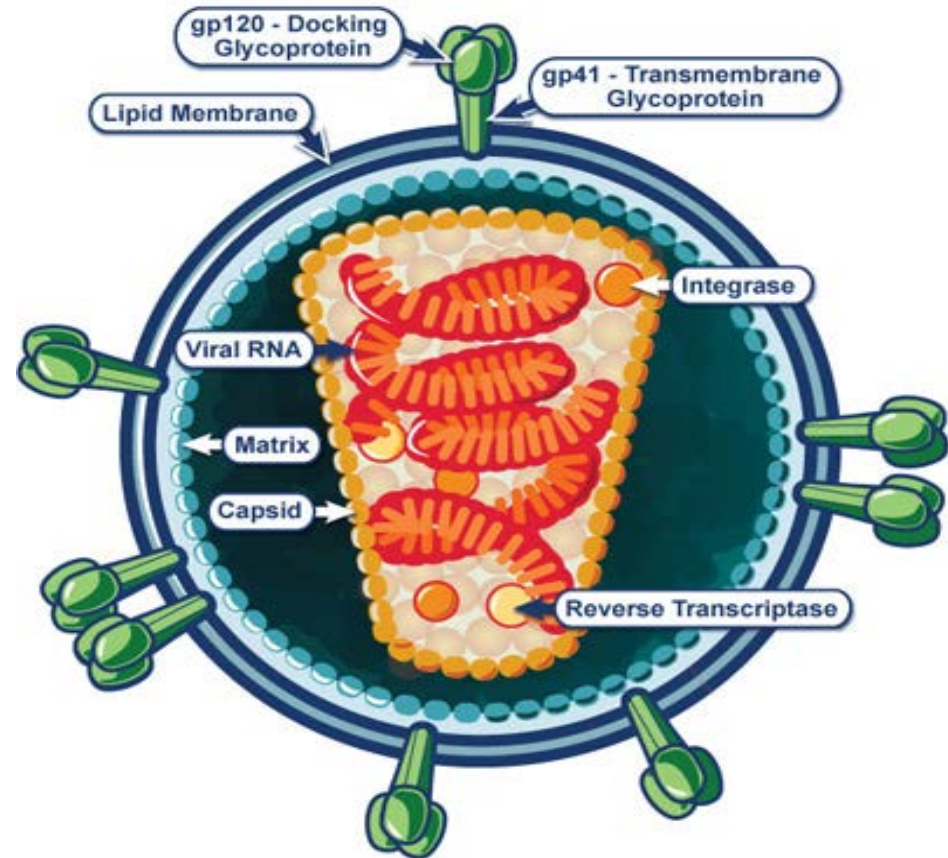
Level of evidence by endpoint

Summary of preliminary level of evidence conclusions



HIV-1 Properties

- RNA virus of the family *Retroviridae*
- Composed of a lipid membrane envelope
- Surrounds a protein matrix
- Protein capsid with 2 copies of the ssRNA genome and enzymes
- Virion infects CD4 cells, B cells, monocytes, macrophages and follicular dendritic cells

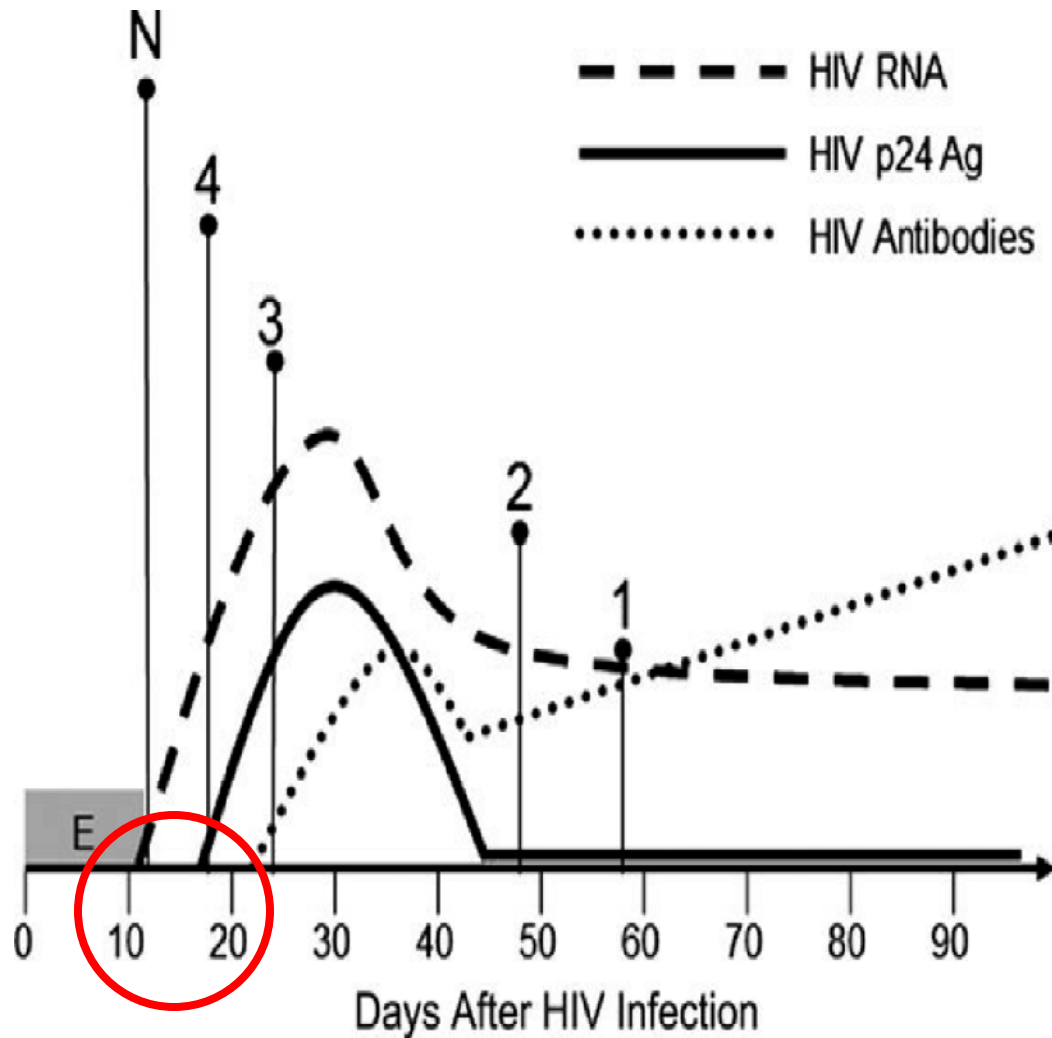




- RNA viral load and infectiousness very high after initial infection
- Immune response produces CD8 killer T cells, killing infected CD4 cells, resulting in decreased HIV-1 titers
- HIV remains latent integrated in the host genome, with low HIV titers
- 10-12 years before symptoms occur, but latency can vary 2-25 years



HIV-1 Detection



- HIV-1 detected in blood and sexual fluids
- HIV RNA can be detected as early as 10 days



Transmission – Sexual Fluids, Blood, *In Utero*

- Transmission occurs
 - During sexual activity
 - Through sharing of infected needles
 - Vertically: *in utero*, during birth, and through breastfeeding
- Highest transmission rates occur in populations practicing unprotected sex and sharing contaminated needles
- Other sexually transmitted infections (e.g., chlamydia and gonorrhea) can increase risk of transmission



Significant HIV-1 Exposure

Worldwide – 37M infected; prevalence widely variable across globe

U.S. – 1.2 million infected persons (0.5%)

50,000 new infections/year

- 63% MSMs (men who have sex with men)
- 8% IDUs (injecting drug users)
- 20% Women

13% unaware of infection status

65% untreated - varies by location; accounts for 90% of new infections*

Overall rate – stable; risky behaviors increasing (unprotected anal sex and needle sharing); rate rising in young black and hispanic gay men*

660,000 deaths in persons with AIDS in the U.S. since 1981

*JAMA December 2, 2015 article



Immunosuppression

Lines of evidence supporting an indirect mechanistic link between HIV-1 infection and cancer:

- Similar pattern of increased risk in HIV-1+ persons and immunosuppressed transplant recipients
- Increased cancer risk with decreased CD4 levels or increased HIV RNA load
- Changes in cancer risk from pre- to post-HAART (highly active anti-retroviral treatment) eras
- Increases in infection-related cancers which would suggest diminished immune surveillance.
- 70% of the cancers in HIV+ are infection related (HPV, HCV, HBV, EBV) compared to 12% in HIV- populations.



Mechanisms incompletely understood

- Chronic inflammation may contribute to malignant transformation
- Traditional risk factors (e.g., smoking, alcohol) higher in HIV/AIDS populations
- Evidence for direct oncogenesis unclear
 - Tumor cells do not harbor HIV-1 proviruses
 - HIV-1 or its transcripts alone do not transform cells
 - HIV-1 RNA levels associated with AIDS defining malignancies
 - HIV-1 proteins
 - Interact with oncogenic viruses
 - Disrupt cell-cycle regulation
 - Inhibit tumor suppressor genes and DNA repair
 - Promote chromosome instability



HAART – Highly active anti-retroviral therapy

- In use since 1996 to treat HIV+ persons; combines different classes of medications based on viral load, viral strain, CD4+ cell count, and symptoms
- Does not eliminate virus, but controls viral load, and prevents or delays symptoms or progression to AIDS, prolonging survival

Concern for potential carcinogenicity

Human studies

↑↓ Inconsistent reports of increase in non-nucleoside reverse transcriptase inhibitors from 3 studies, with 1 study finding marginal ↑ in anal cancer with long-term use

HAART does not explain excess risk of cancer in HIV+ individuals

Animal studies

IARC 2000 concluded Zidovudine (AZT) And Zalcitabine (DDC) *possibly carcinogenic* based on sufficient evidence in animals

NTP found certain single drugs and mixtures to induce chromosomal damage, gene mutations, cancer after direct exposure in F1 p53^{+/-} mice; and liver cancer and subcutaneous skin neoplasms after *in utero* and postnatal gavage exposure



NTP Literature Search Strategy

- Focused search for cohort studies and reviews from 2009-2015
 - Identified 21 cohort or record-linkage studies (risk estimates for 3+ cancer sites); additional studies of specific cancers
- Evaluated consistency of new data published since 2008 with IARC (2012)
 - AIDS defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, cervical)
 - Hodgkin lymphoma
 - Invasive anal
 - Conjunctival
- Conducted a review of cancer sites with inadequate data or data gaps by 2008
 - Genital (vaginal/vulvar, penile)
 - Oral
 - Non-melanoma skin
 - Lung
 - Hepatocellular



Cancers Associated with HIV-1+

AIDS defining cancers (considered to be diagnostic criteria for AIDS)

Kaposi Sarcoma

Non-Hodgkin lymphoma

Invasive Cervical

Non-AIDS defining cancers, infection related (caused in part by co-infection with known oncogenic viruses)

Hodgkin lymphoma

Invasive anal cancer

Genital (Vaginal/vulvar, penile)

Oral

Non-AIDS defining cancers, not infection related (cancers not thought to be AIDS defining or infection related)

Conjunctival

Non-melanoma skin cancer

Lung cancer

Hepatocellular cancer



Sufficient Level of Evidence

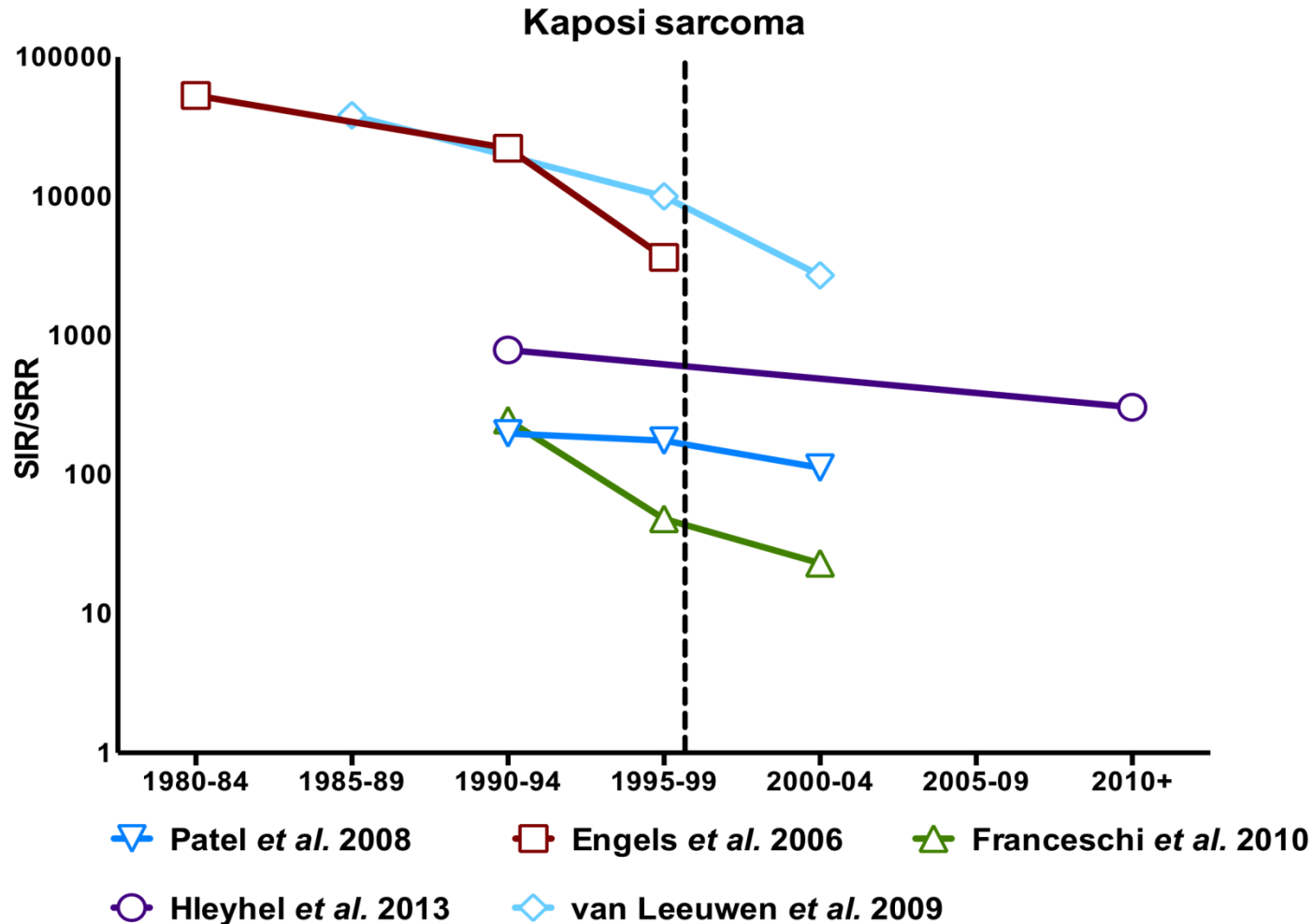
	# Studies 2008/2009 +	RR/SIR range**	mRR/ mSIR**	Viral co- factor	Cancer risk in HAART era	CD4 and cancer risk
Kaposi sarcoma	22/16	100- 10,000's	3640 (3326- 3976)	KSHV	↓ 5 cohorts	Significant D-R ↑
NHL	21/16	10-300	77 (39- 149)	EBV in some subtypes	↓ 7 cohorts	Significant D-R ↑
Cervical cancer	17/15	2-25	5.8 (3- 11.3)	HPV	↑↓	↑↓
Hodgkin lymphoma	23/18	4-38	11 (8.8-15)	EBV 80- 100% of cases	↑ RR	Significant ↓ with most recent CD4
Anal cancer	17/21	9-39	28.8 (21.6-38.3)	HPV	↑↓	↑↓
Conjunctival cancer	6/2	12-15	6.2 (4.8-7.9)	UV	↑↓	↑↓

*Number of studies = reviewed by IARC/reviewed by NTP; **range reported by IARC; ***meta-analyses = Grulich *et al.* 2007 and Shiels *et al.* 2009; RR = relative risk; SIR = standardized incidence ratio; CI = confidence interval; NHL = non-Hodgkin lymphoma.



Decreased Risk of Kaposi Sarcoma with HAART

Declines in HIV/AIDS cohorts pre-HAART (1980-1996) to HAART (1996-on)





Infection related

- *Genital cancers – vaginal, vulvar, penile*
- *Oral cancer*



Sufficient Level of Evidence

Genital cancers

	# Studies 2008/2009 +	RR/SIR range**	mRR/ mSIR**	Viral co- factor	Cancer risk in HAART era	CD4 and cancer risk in HAART era
Vaginal/vulvar	7	5-7	9.4 (4.9- 8)	HPV	↑↓ 2 cohorts	Low CD4 at AIDS onset assoc. with high risk
Penile	6	4-28	6.8 (4.2-11)	HPV	↑↓ 2 cohorts	NR

Higher risks for *in situ* vs. invasive cancers (~20-fold)

Similar risk estimates across IDUs, MSMs, heterosexuals

*Number of studies = reviewed by IARC/reviewed by NTP; **range reported by IARC; ***meta-analyses = Grulich *et al.* 2007 and Shiels *et al.* 2009; RR = relative risk; SIR = standardized incidence ratio; CI = confidence interval; NHL = non-Hodgkin lymphoma.



Limited level of evidence from human studies

- Oral cavity cancers and oropharyngeal cancers
- RR – modest consistently increased risk of 2 to 4 across various groupings of oral cancers; 19+ cohort studies
- mSIR = 2.3 (95% CI = 1.6 to 3.2) (Grulich *et al.* 2007)
- Issues for consideration
 - Endpoint heterogeneity – different types of oral cancers
 - Viral cofactors - Oncogenic HPV necessary in some types of cancers (HPV associated vs. HPV non-associated)
 - Inconsistent evidence of HIV-mediated immunosuppression (CD4)



Unmeasured variations in cohorts may explain modest risks

- Differences in transmission dynamics of HPV between males and females may explain lower risks in HIV/AIDS cohorts with high % of MSMs
- Unmeasured variations across cohorts in sexual behaviors may influence the % of HPV-associated cancers in any cohort
- Tobacco and alcohol, both more prevalent in HIV/AIDS populations, not adequately investigated
- Smoking controlled in models resulted in crudeSIR = 1.9 (sig.) → adjSIR = 1.4 (ns) (Silverberg 2011)



Not infection related

- *Non-melanoma skin cancer*
- *Lung cancer*
- *Liver cancer*



Sufficient level of evidence from human studies

- RR – consistently increased risk 1.5 to 6, some up to 20-fold; 19+ studies
- mRR = 2.76 (2.55 to 2.98) 6 cohorts verifying diagnosis via cancer registry (Zhao *et al.* 2015)
- Increased risk associated with high HIV-1 RNA and low CD4 counts
- Most common subtype: basal cell carcinoma
- Viral cofactors – Potential role for rare Merkel cell carcinoma polyomavirus increased in HIV-1 + persons; overall contribution to risk of non-melanoma skin cancer unknown



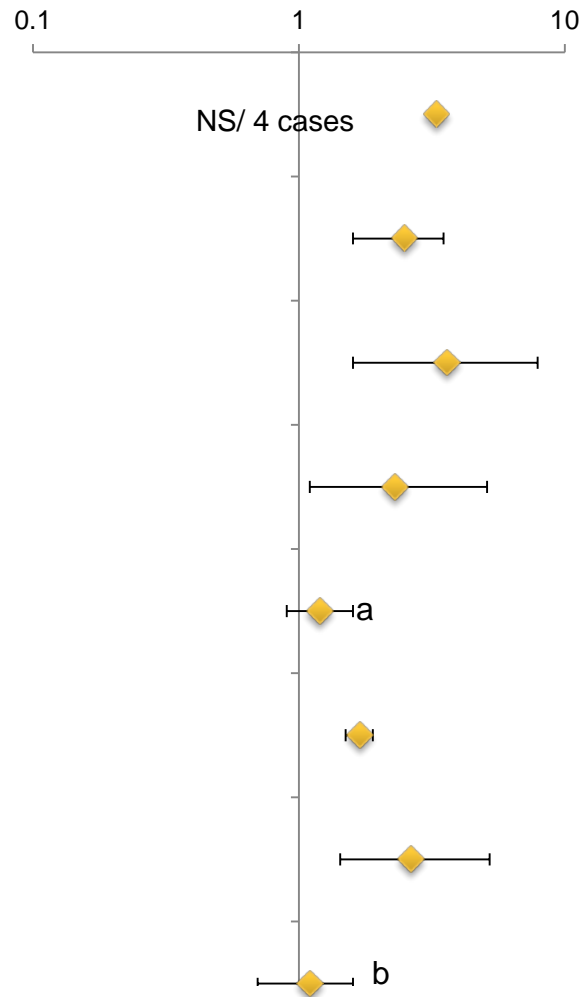
Sufficient level of evidence from human studies

- RR – consistently increased risk 1.5 to 6; 48+ cohort studies
- mRR = 2.6 (95% CI = 2.1 to 3.1) (Shiels *et al.* 2009)
- Inconsistent association between CD4 and viral load with risk
- Risk is increased in the HAART era (mSIR = 2 to mSIR = 3.5)
- No known viral cofactors
- Cancer subtypes
 - Adenocarcinoma most frequent in HIV+ persons, appears at advanced stages, younger age
 - Small cell carcinoma commonly associated with smoking
 - Smoking is 2-3x more prevalent in HIV+ vs. general population



Smoking Adjustment in Studies of HIV-1 and Lung Cancer

Reference	Population	Smoking
Phelps 2001 Incidence	HIV Epi Research Study – HIV+/- Women	No details
Engels 2006b Incidence	Moore Clinic Cohort HIV+ and SEER General Pop	Indirect smoking adjustment; sensitivity analysis
Kirk 2007 Mortality	ALIVE IDU Cohort HIV+ and HIV-	Pack-yr/day; cumulative Pack-yrs
Shiels 2011 Incidence	HIV/AIDS Cancer Match Study	Pack-yr/day
Silverberg 2011	Kaiser Permanente HIV+ and HIV-	baseline tobacco use
Sigel 2012	VACS-VC Veterans HIV+ and HIV-	Smoking status
Hessol 2015	WHIS and MAC HIV+ and HIV-	Pack yrs smoking
Stein 2008	South Africa Case-control	Smoking status



^aSignificant adjusted RR among those with low CD4 cells; ^bNo excess risk in unadjusted analysis.



Limited level of evidence from human studies

- RR – consistently increased risk of 2 to 16; 40+ cohort studies
- mSIR = 5.6 (95% CI = 4.0 to 7.7); (Shiels *et al.* 2009)
- Inconsistent evidence for changes in risk from pre- to post-HAART eras –increased, decreased, or similar risks over time.
- Viral cofactors – HCV, HBV



Unclear if HCV/HBV are confounders or viral co-factors

- Few studies have measured seroprevalence of viral co-factors
- Variations in risk with HAART may be due to differing prevalence of HCV in cohorts, long term survival into older ages when cancer is more common, or other risk factors
- Several studies report no association between HIV and HCC among those with HCV infection or after adjustment for HCV
- HCV+ persons (mono-infected) had higher risk of liver cancer than those co-infected with HIV-1 (incidence ratio = 1.97) (DiBenedetto 2014)
- Unclear if HCV is a confounder or acts as a viral co-factor



- 3900 cancers occur in HIV+ persons (2010)
- 90% of these cancers are included in NTP HIV-1 monograph
- 10% include other cancers potentially related to HIV-1
 - 8 additional cancers had RR = 1 to 2 (Shiels *et al.* 2009) based on at least 70 cases in at least 3 studies
 - non-AIDS, non-infection-related cancers have significantly increased in HIV-1+ persons ~2-fold (Albini *et al.* 2013)
 - Smoking related cancers in HIV+ persons are increased ~3-fold (Helleberg *et al.* 2015)
 - Increased risk of these cancers could be due directly to HIV-1, survival, or to behaviors/confounders common among HIV-1+ persons
- Pre-cancers are also an important burden for HIV-1+ individuals



HIV-1 Preliminary Level of Evidence Summary

Sufficient evidence

AIDS defining

- Kaposi sarcoma
- Non-Hodgkin lymphoma
- Invasive cervical cancer

Non-AIDS defining, infectious

- Hodgkin lymphoma
- Invasive anal cancer
- **Genital (vulvar, vaginal, penile) cancer**

Non-AIDS defining, not infectious

- Conjunctival cancer
- **Non-Melanoma skin cancer**
- **Lung cancer**

Limited evidence

Non-AIDS defining, infectious

- **Oral cancer**

Non-AIDS defining, not infectious

- **Liver (hepatocellular) cancer**



Clarifications?



All sections: Comment on whether the information is clear and technically accurate and identify any information that should be added or deleted,

Properties, Detection and Human Exposure

- and whether adequate information is presented to document past and/or current human exposure.

Human Cancer Studies

- and provide any scientific criticisms of NTP's cancer assessment of the epidemiologic studies of exposure to the virus.

Mechanistic and Other Relevant Data

- and provide any scientific criticisms of the NTP's synthesis of these data assessing effects of the virus.



Sufficient evidence of carcinogenicity from studies in humans

- Cancer sites with sufficient evidence
 - Kaposi sarcoma
 - Non-Hodgkin lymphoma
 - Hodgkin lymphoma
 - Invasive cervical cancer
 - Invasive anal cancer
 - Genital cancers (vaginal/vulvar and penile)
 - Conjunctival cancer
 - Non-melanoma skin cancer
 - Lung cancer



Limited evidence of carcinogenicity from studies in humans

- Cancer sites with limited evidence
 - Liver cancer
 - Oral cancer



Preliminary Listing Recommendation (Vote)

HIV-1

Human immunodeficiency virus type 1 (HIV-1) is *known to be a human carcinogen* based on sufficient evidence from studies in humans.

This conclusion is based on epidemiological studies showing that HIV-1 increases the risk of Kaposi sarcoma, non-Hodgkin lymphoma, invasive cervical cancer, Hodgkin lymphoma, invasive anal cancer, genital cancers (vaginal/vulvar and penile cancers), conjunctival eye cancer, non-melanoma skin cancer, and lung cancer, together with supporting evidence from mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans.

Epidemiological studies also provide limited evidence for an association between HIV-1 infection and oral and liver cancer.



- Contains NTP's preliminary recommendation of the listing status of the substance
- Summarizes the scientific information that is key to reaching a recommendation
- Provides information on properties, use, production and exposure
- Provides information on existing federal regulations and guidelines



Peer Reviewer Comments

- Provide any new comments (e.g., not previously provided on the same facts or issues in the cancer hazard evaluation section) on whether the information on properties and detection, human exposure, cancer studies in humans and mechanistic data is clear and technically accurate.
- Comment on whether the substance profile highlights the information on cancer studies in humans and mechanistic data that are considered key to reaching the listing recommendation.