MALIGNANCIES IN PEOPLE WITH HIV/AIDS

MARK POLIZZOTTO | ASHM ANNUAL MEETING | PERTH, SEPTEMBER 16, 2019

OUTLINE

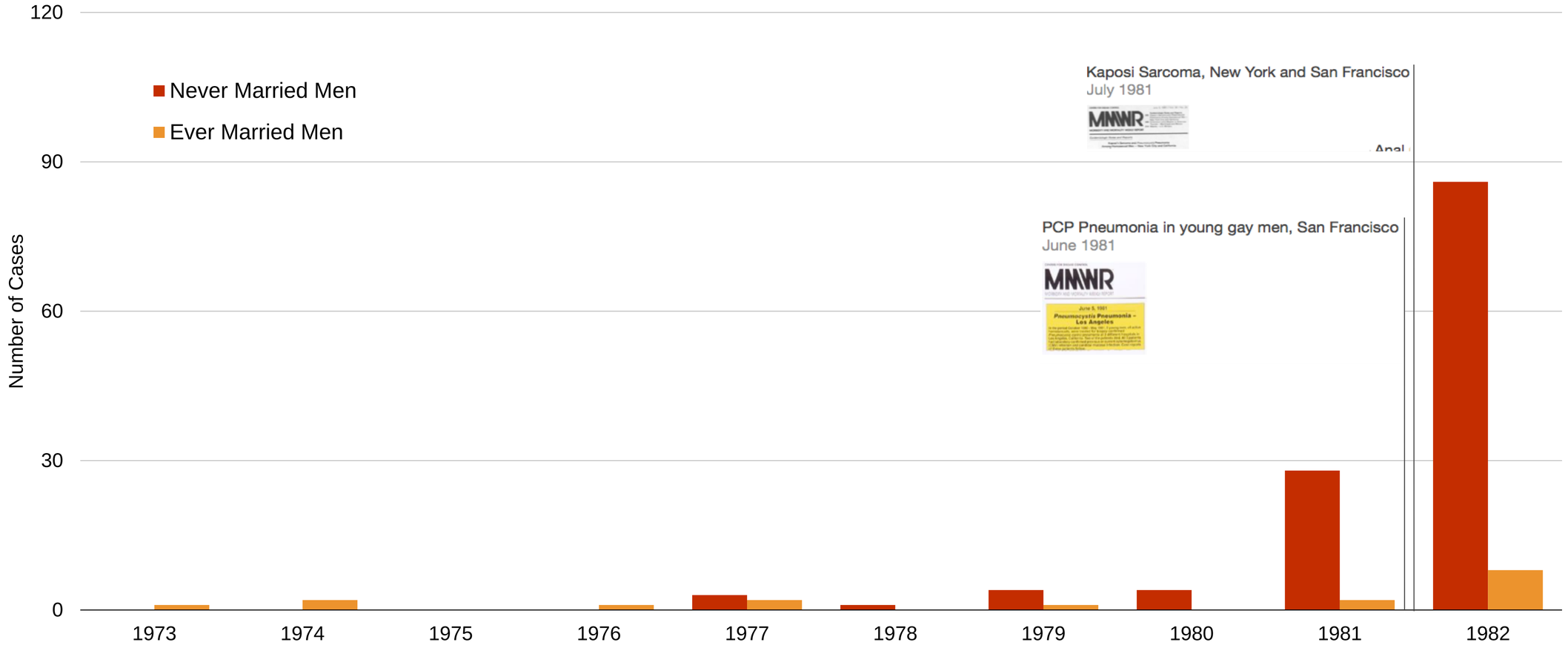
POPULATION TRENDS

PREVENTION

THERAPY

POPULATION TRENDS

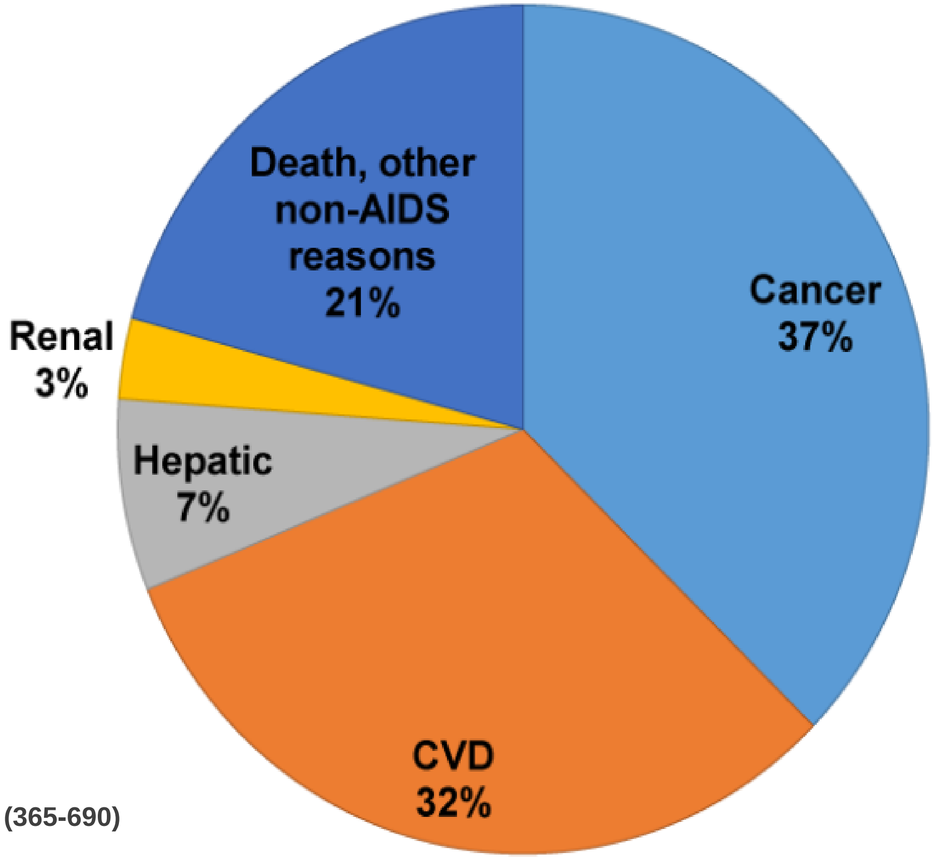
KAPOSI SARCOMA INCIDENCE



Source: New York State Cancer Registry

CONTINUING COMORBIDITIES

Serious Non-AIDS events in Continuous ART Groups from INSIGHT studies



CD4 median (IQR) = 500 (365-690)

Composition of SNA/death	
Components	**Overall**
CVD	82
Cancer	97
Hepatic events	19
Renal events	8
Death, other causes	54
Any SNA/death	**260**

Grund, Baker, Deeks, et. al. Plos One 2016

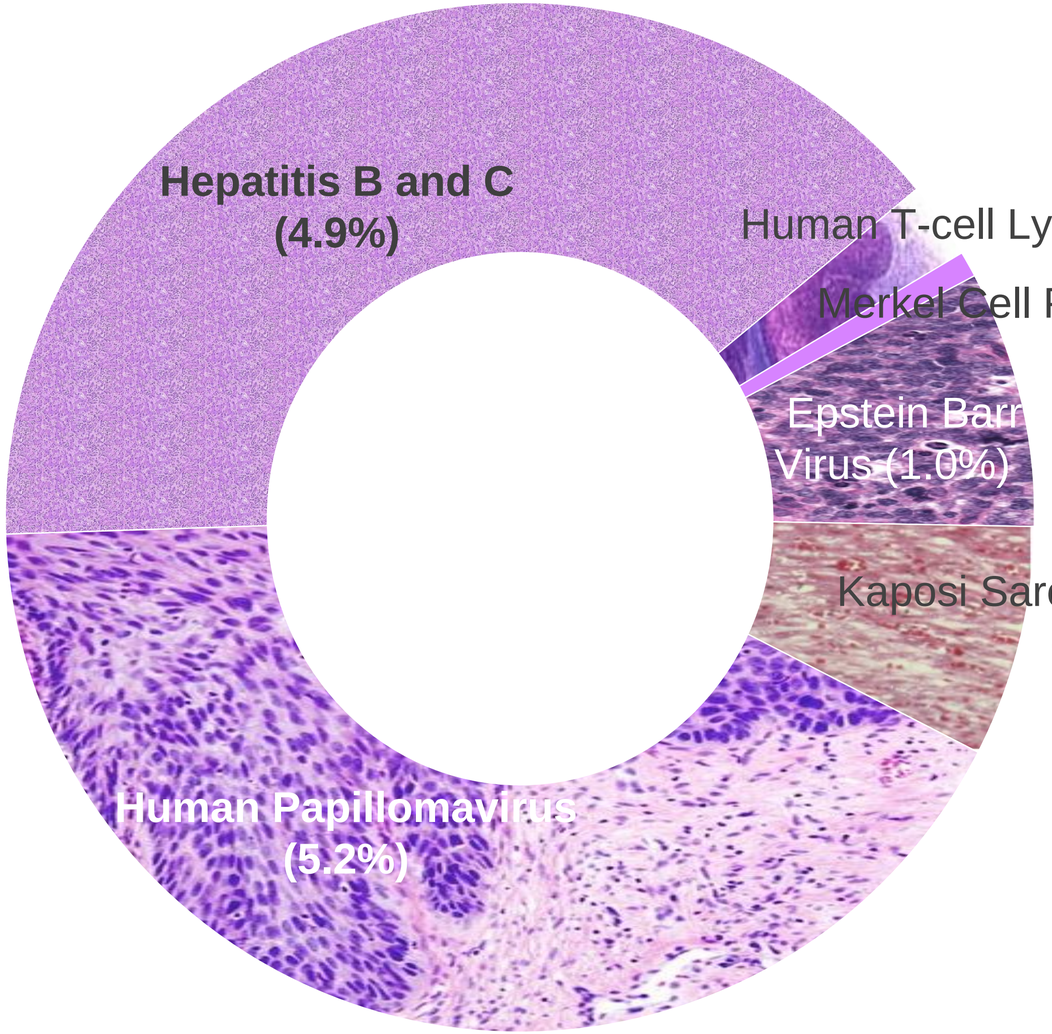
MALIGNANCIES IN PEOPLE WITH HIV

Malignancy	Incidence (per 100,000 PY)	Standardised Incidence Ratio	Proportion Occurring in People with HIV/AIDS
All Cancer Types	468	**2.1 (2.0-2.3)**	
AIDS Defining Cancers			
Kaposi sarcoma	173	1300 (1100–1500)	81.6% (81.2%-81.9%)
Diffuse large B-cell lymphoma	50	9.6 (7.7–12)	6.0% (5.8%-6.1%)
Burkitt lymphoma	7	15 (7.9-27)	19.9% (18.1%-21.7%)
Primary CNS lymphoma	15	250 (160–360)	27.1% (26.1%-28.1%
Invasive cervical cancer	44	2.9 (1.9-42)	0.42% (0.37%-0.47%
Non-AIDS Defining Cancers			
Anogenital	10	9.2 (5.5–15)	—
Hodgkin Lymphoma	19	5.6 (3.9–7.8)	—
Head and Neck	14	1.7 (1.1–2.5)	—
Hepatocellular	8	2.7 (1.5–4.6)	—
Lung Cancer	59	2.6 (2.1–3.1)	—
Pancreas	8	2.2 (1.2–3.6)	—

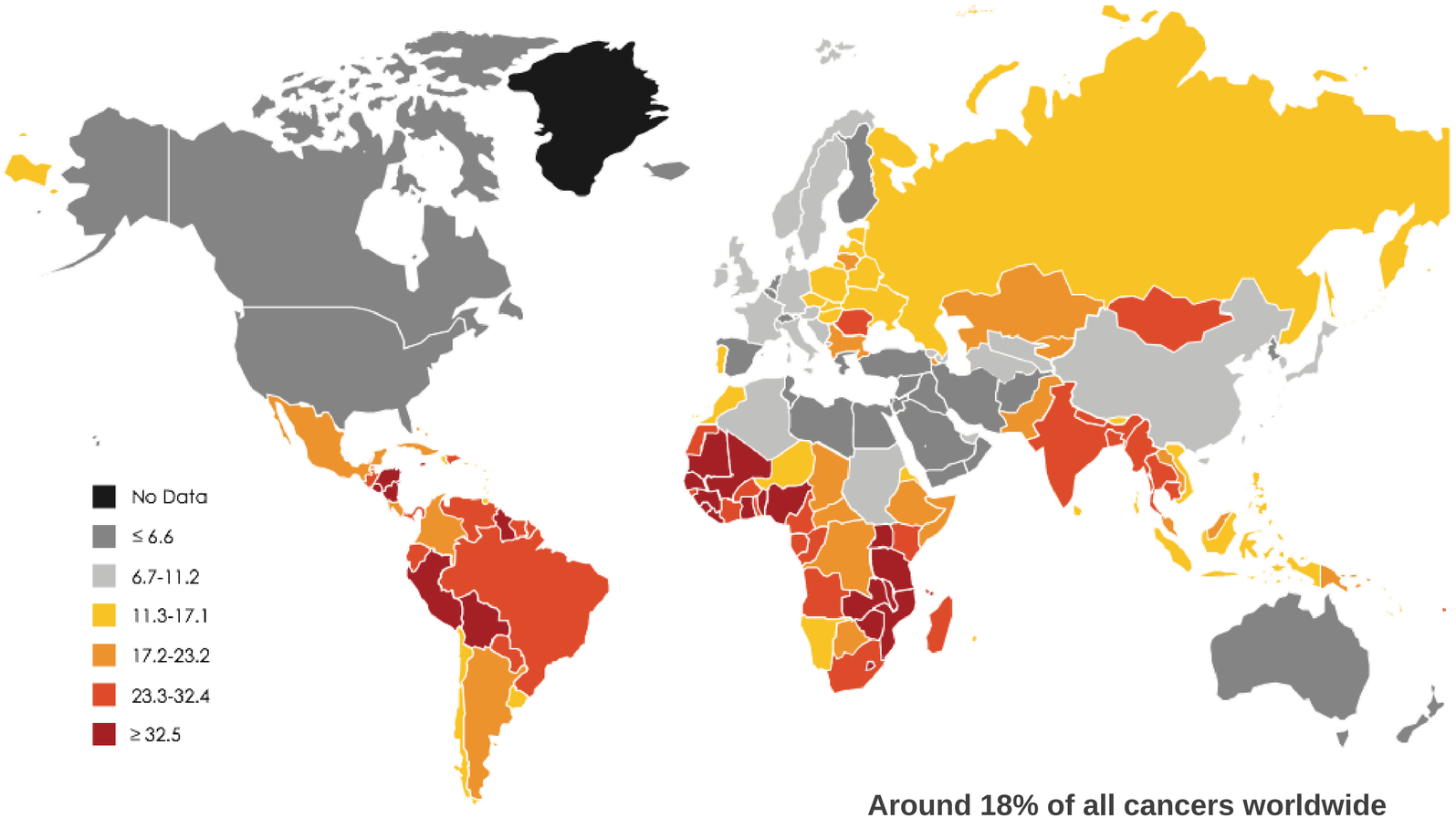
Parkin DM. Int J Cancer 2006;118:3030–3044. Shiels M, JAMA 2011;305:1450-9.

INFECTION RELATED CANCERS

- World Health Organisation estimates:
  - 18% of cancer cases are caused by infection
  - 12% are caused by one of seven human tumour viruses

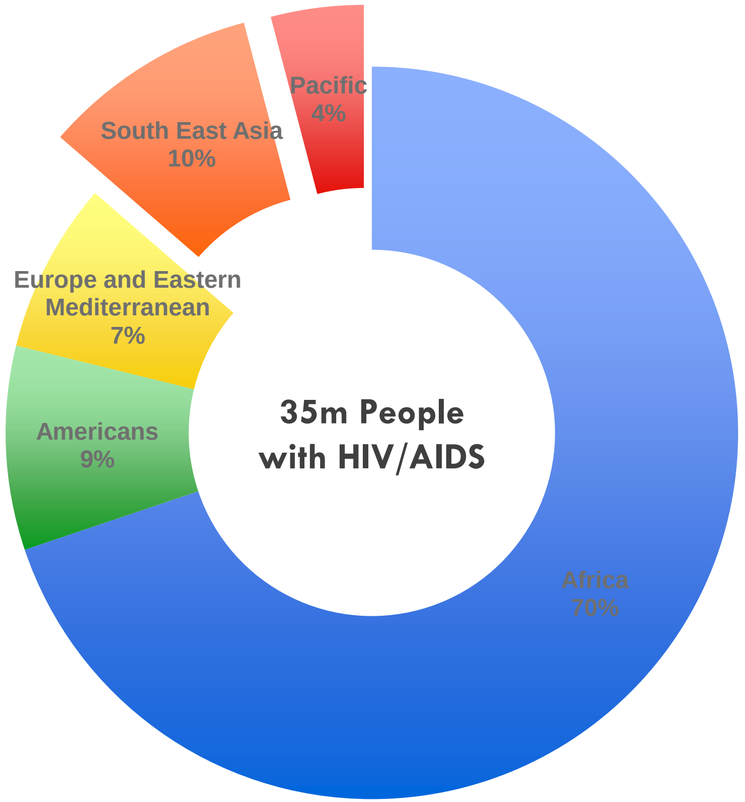


INFECTION RELATED CANCERS



Around 18% of all cancers worldwide
Most common cancers in many resource-limited settings

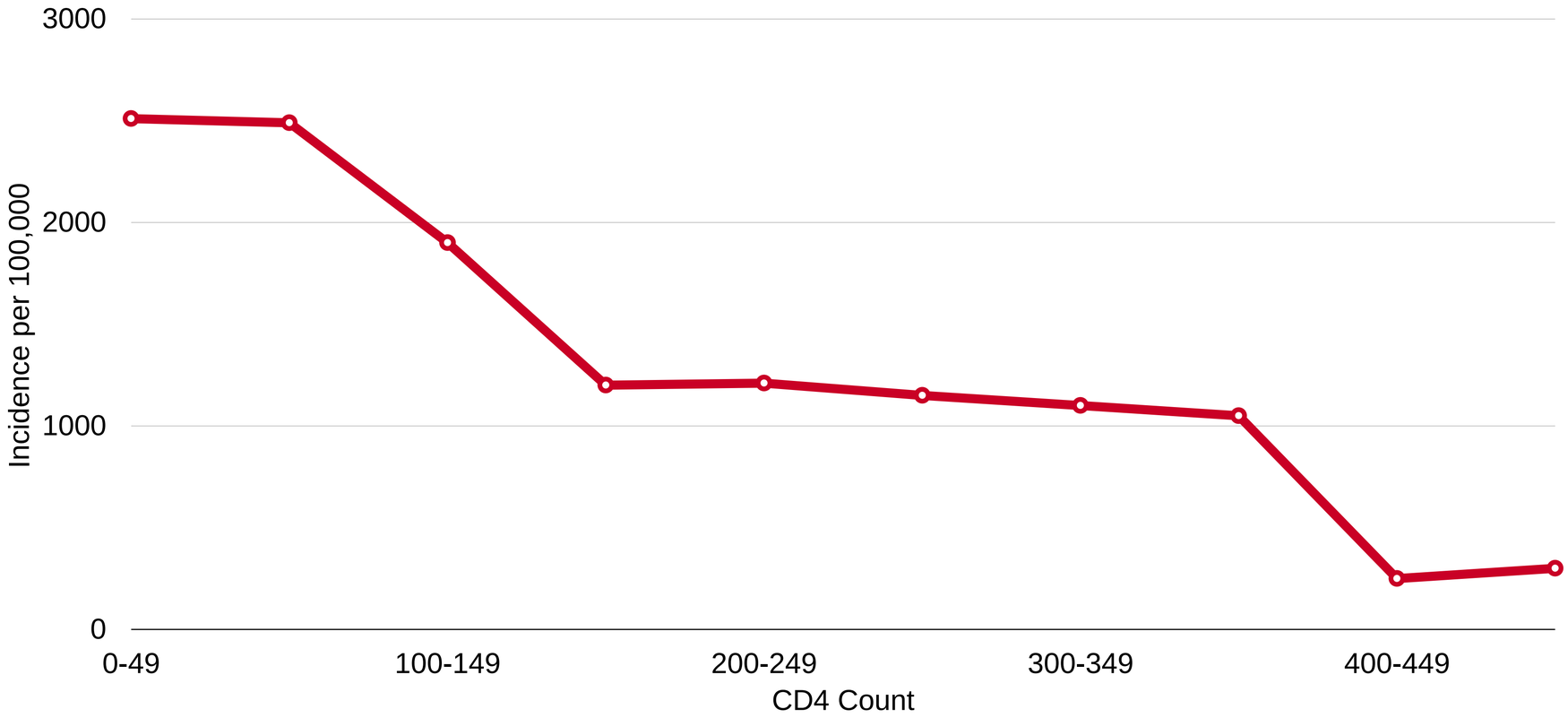
HIV MALIGNANCIES IN ASIA



- No prior systemic data
- Aimed to assess the occurrence, risk factors and survival outcomes associated with malignancies in the TREAT Asia HIV Observational Database
- 195 patients (3%) were diagnosed with a malignancy
  - 69 (1%) haematological malignancies (mostly NHL; 0.08 per 100 person-years, 52% mortality
  - 126 (2%) non-haematological (KS, cervical; 0.17 PYS), 27% mortality
- Risks: age, CD4 count, WHO country income level
- Significant burden, and likely significant under-diagnosis in lower income countries

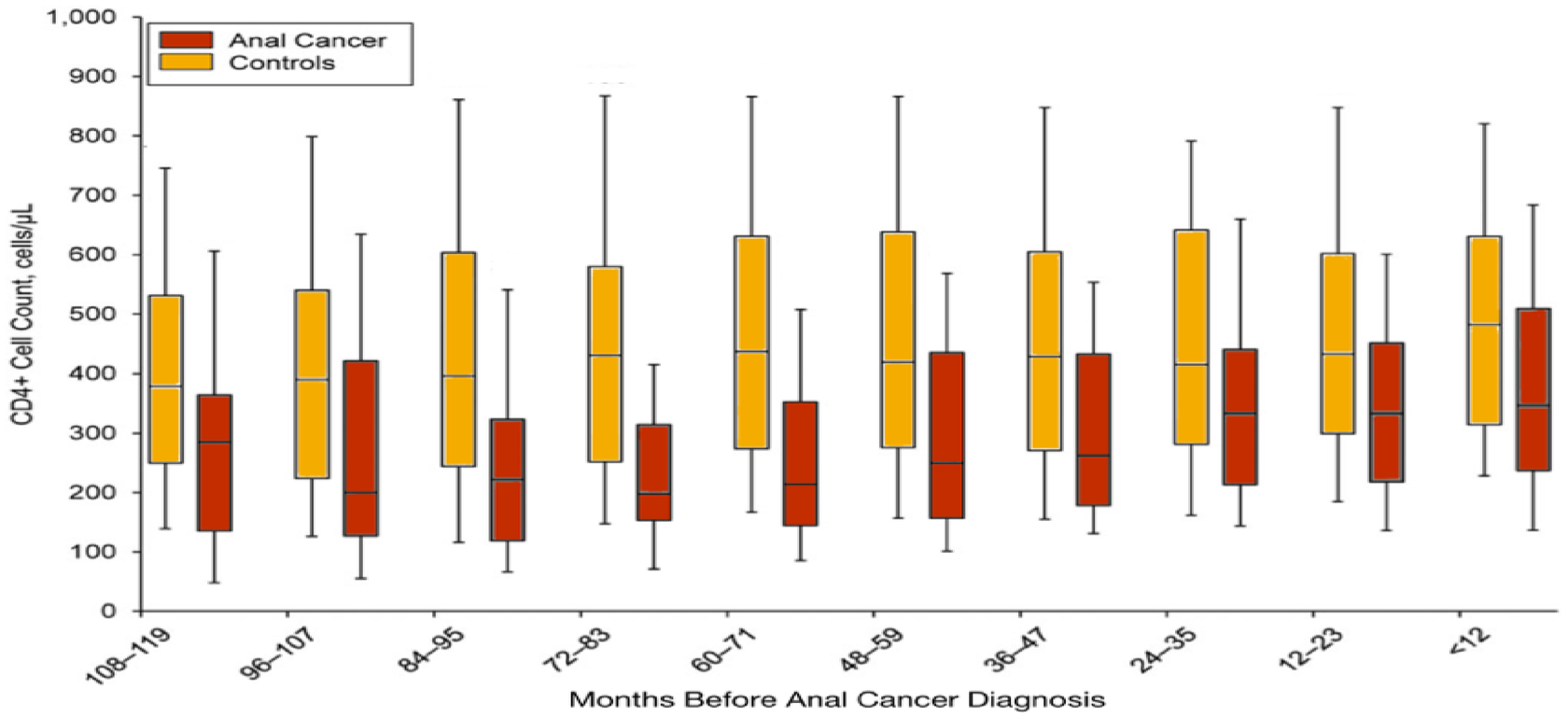
Jiamsakul A, JAIDS 2018 (In Press).

CONTRIBUTORS TO RISK



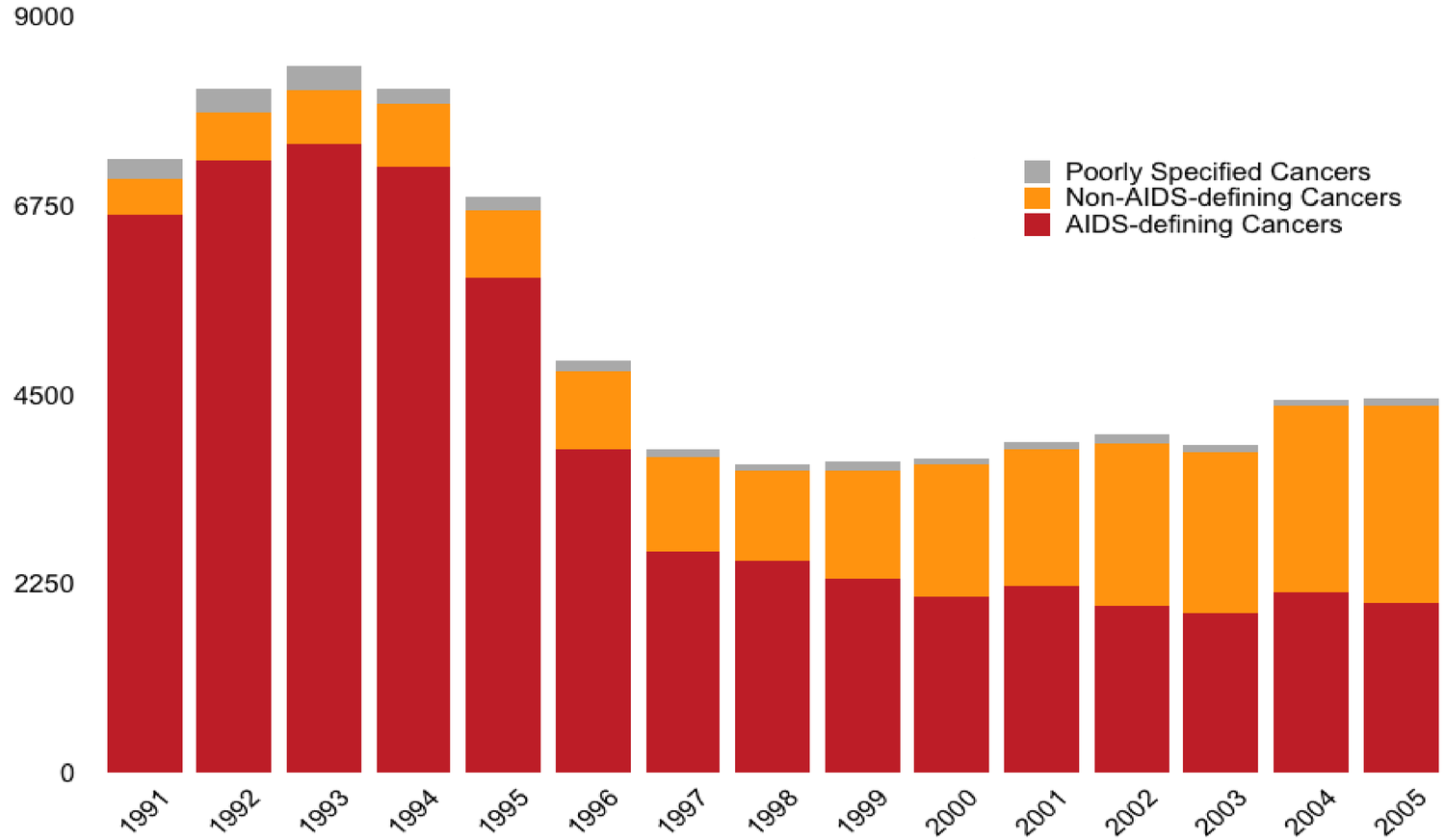
Biggar, R.J et al. J Natl Cancer Inst (2007).

CONTRIBUTORS TO RISK



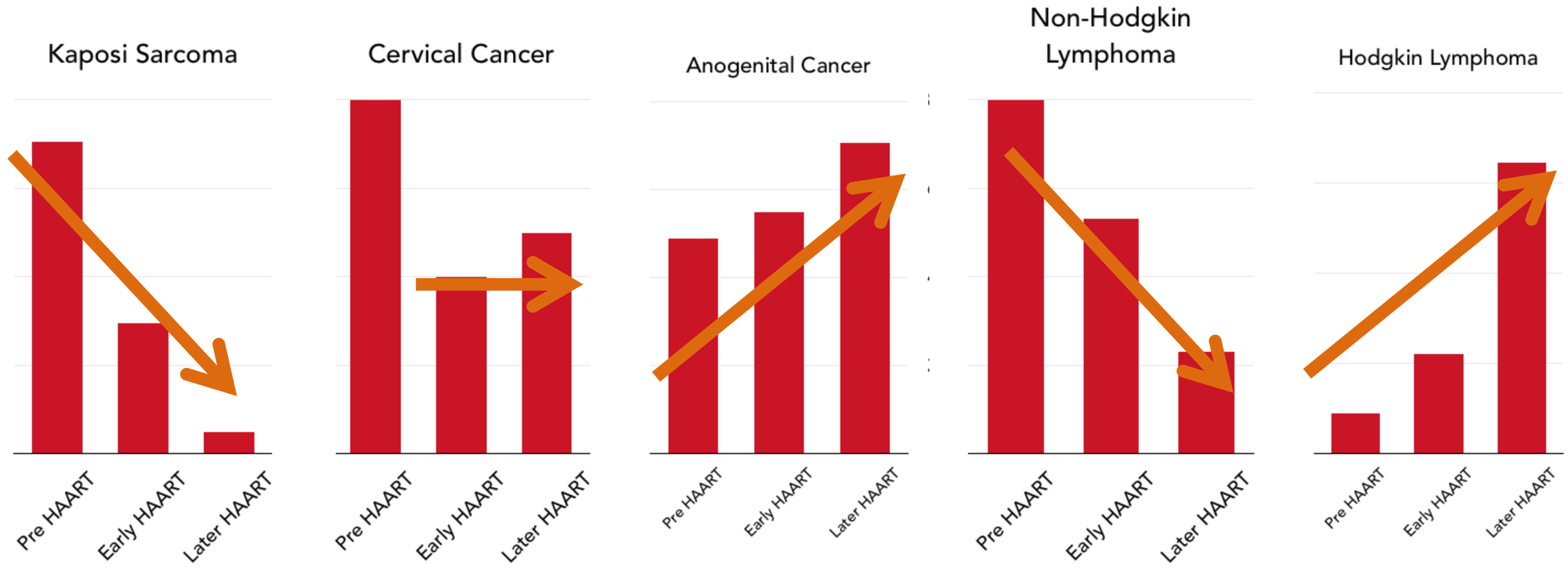
Bertisch Am J Epi 2013

DIVERGENT TRENDS IN INCIDENCE



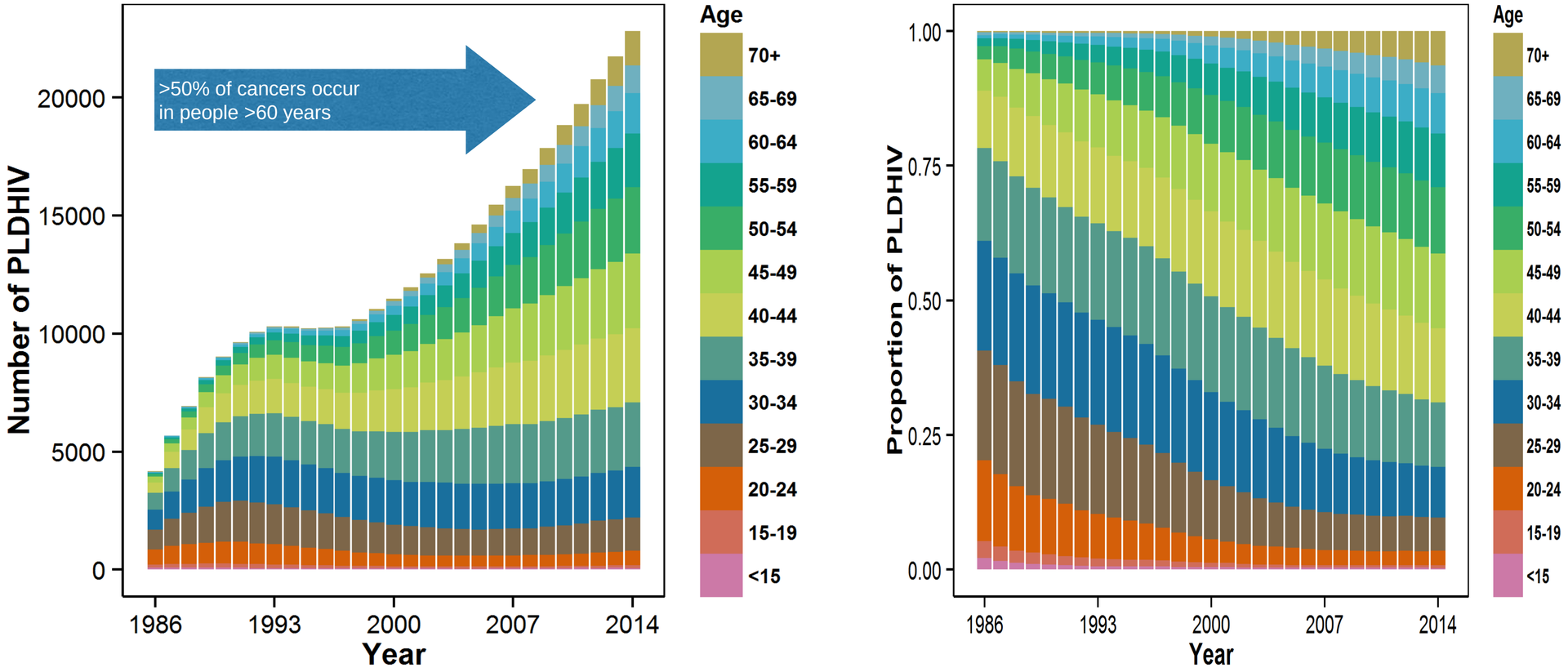
Shield M, JAMA 305: 1450-9 (2011)

DIVERGENT TRENDS IN INCIDENCE



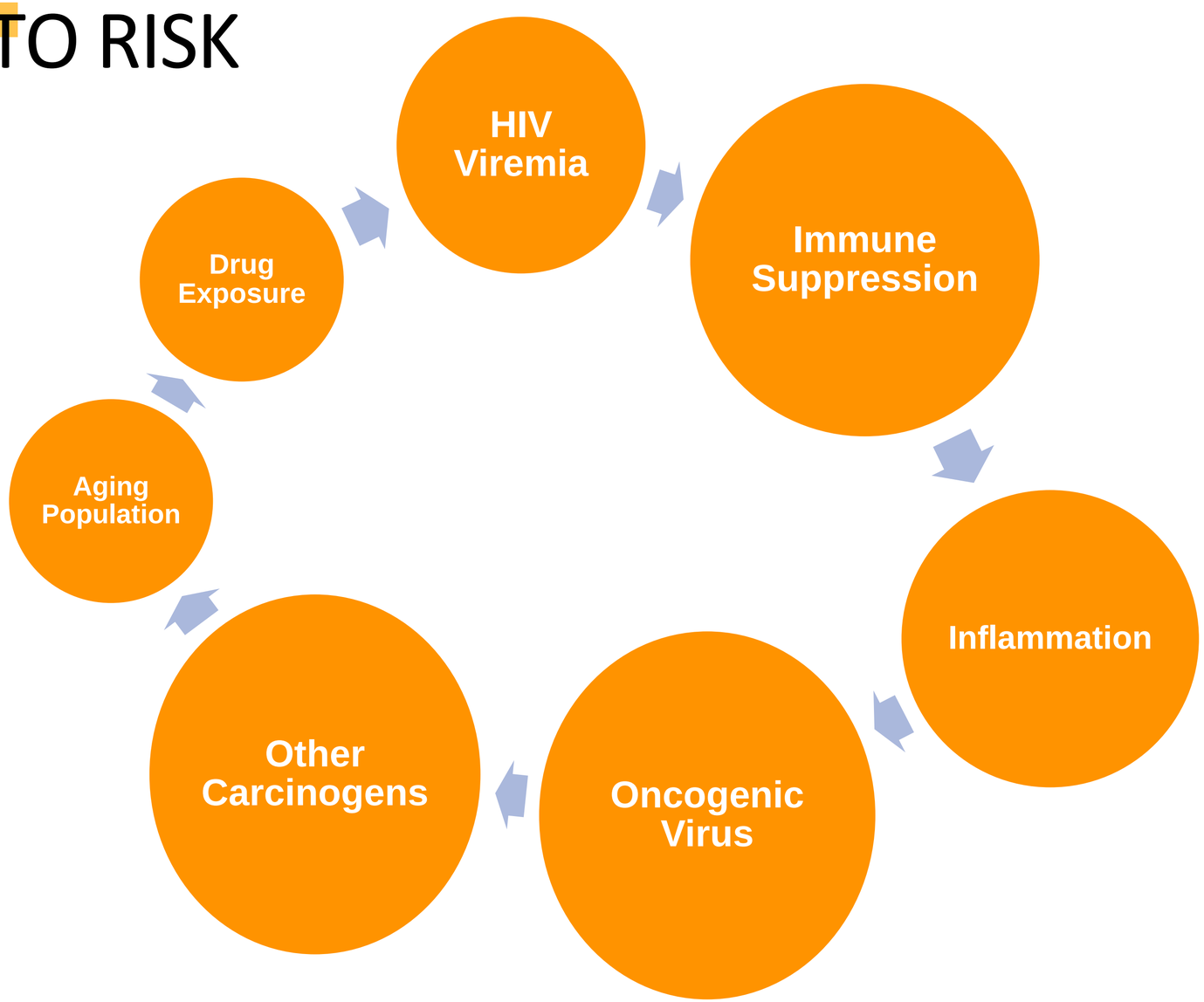
Parkin DM. Int J Cancer 2006;118:3030–3044. Shiels M, JAMA 2011;305:1450-9.

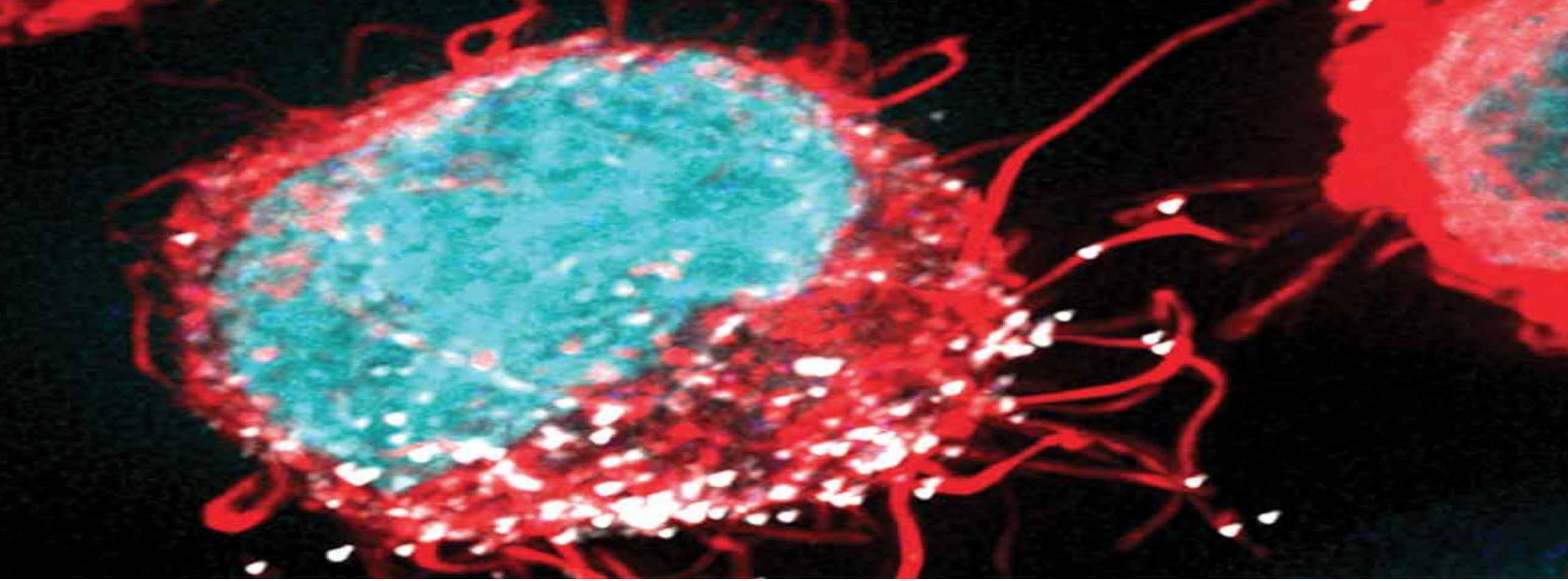
AGING OF PEOPLE WITH HIV



Courtesy Richard Gray, Kirby Institute (Annual Surveillance Report on HIV, viral hepatitis and STIs in Australia 2017, Kirby Institute)

CONTRIBUTORS TO RISK





PREVENTION AND SCREENING

ROLE OF IMMEDIATE ART

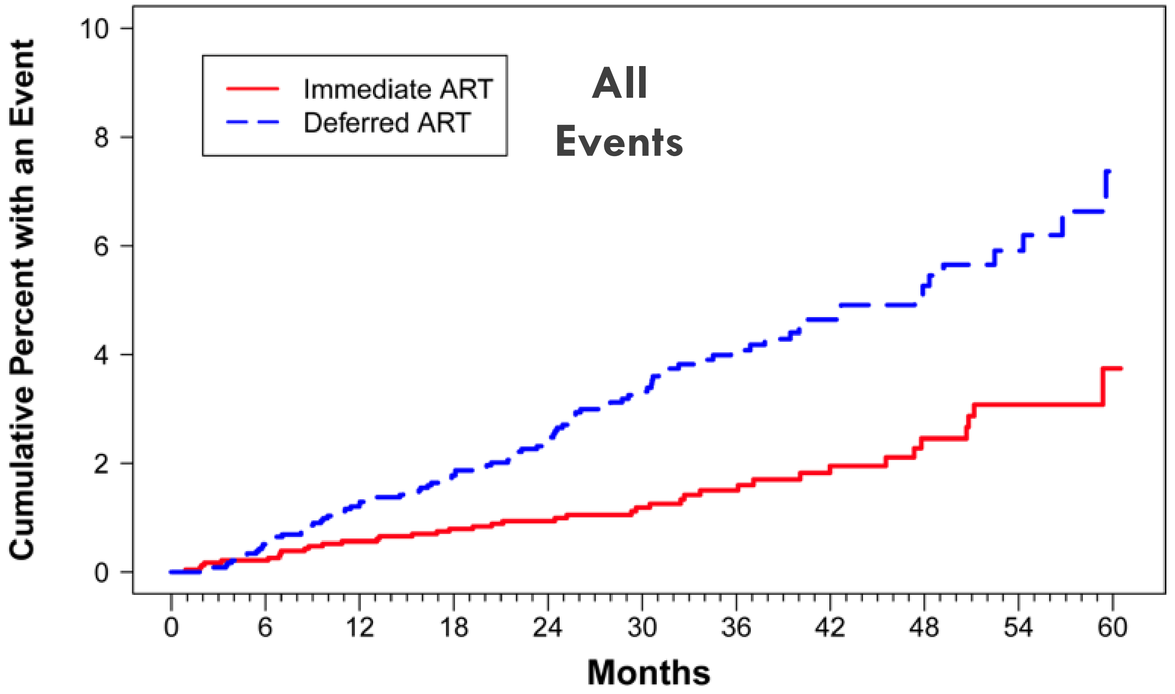
Strategic Timing of Antiretroviral Therapy Trial

Randomised trial of immediate versus deferred therapy:

All with CD4 count of more than 500 at entry

Either: antiretroviral therapy immediately (immediate-initiation group) or
Defer ART until CD4 350 cells or AIDS (deferred-initiation group)

Primary composite end point was any serious AIDS-related event, serious non-AIDS-related event, or death from any cause

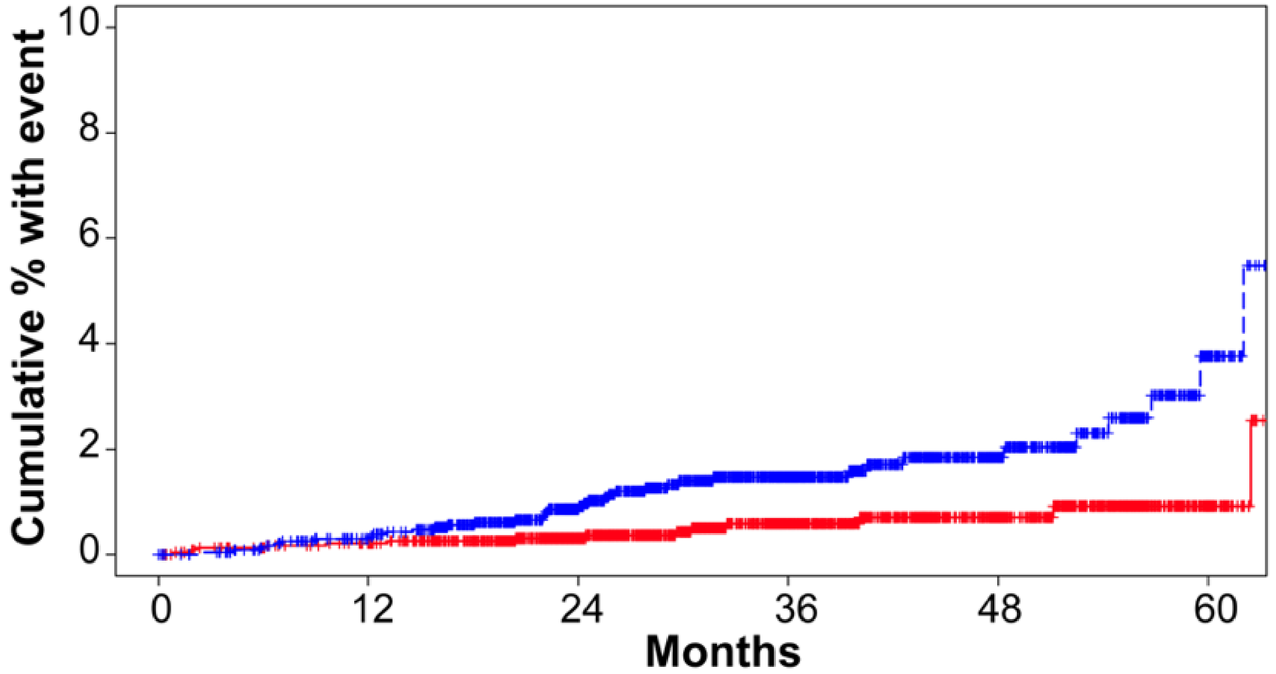


	Immediate ART	Deferred ART
Number (%)	42 (1.8%)	96 (4.1%)
Rate	0.60	1.38
Hazard Ratio	0.43 (95% CI: 0.30 to 0.62, p <0.001)	

INSIGHT START Study Group N Engl J Med 2015;373:795-807.

IMMEDIATE ART PREVENTS CANCER

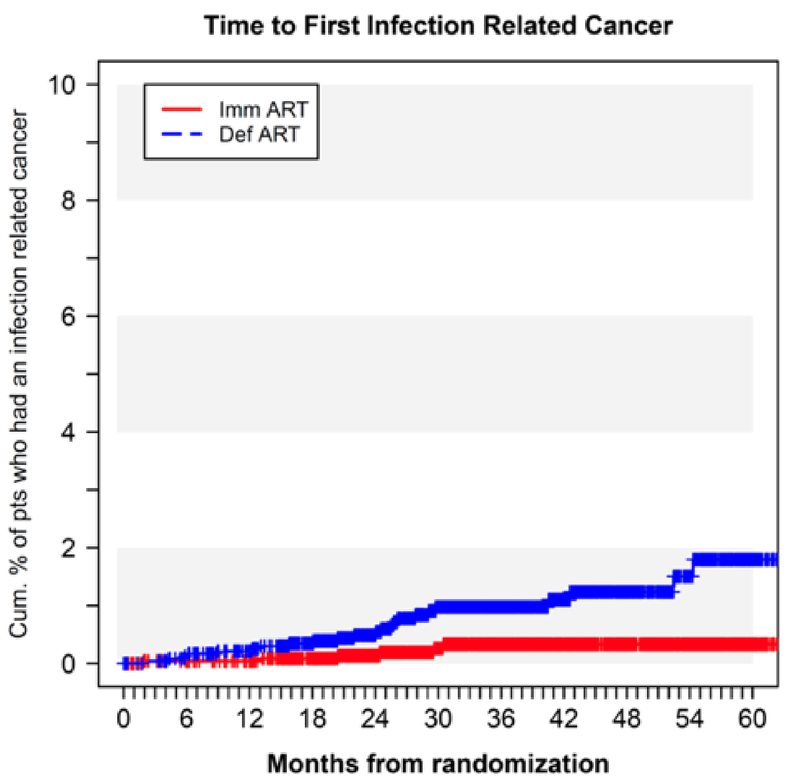
Cancer Events

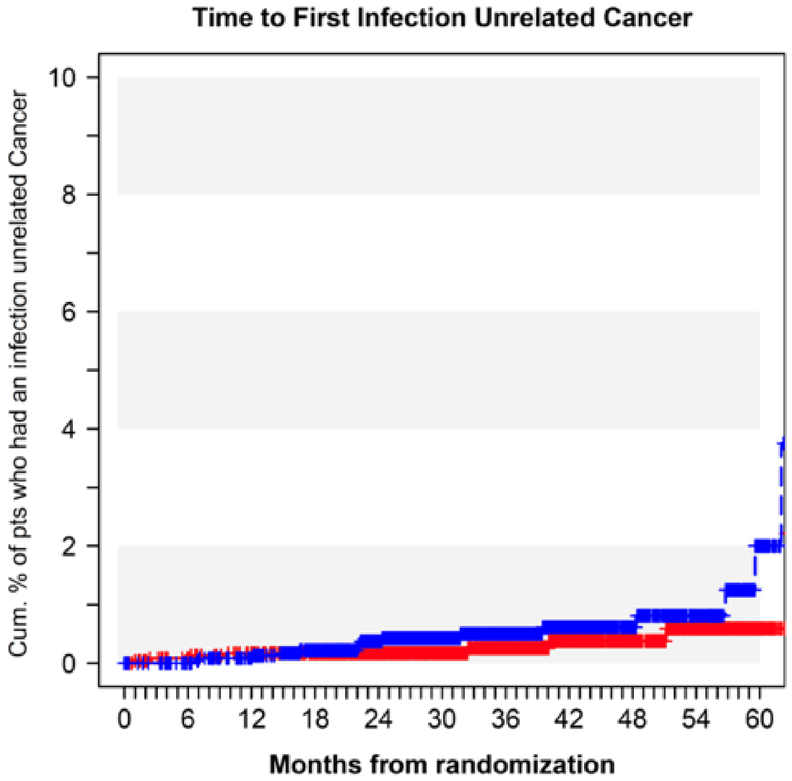


	Immediate ART	Deferred ART
No. with event	14	39
HR (Imm/Def)	0.36 (95%CI: 0.19 to 0.66, p=0.001)	

INSIGHT START Study Group N Engl J Med 2015;373:795-807.

IMMEDIATE ART PREVENTS CANCER





	Immediate ART	Deferred ART
No. with	6	23
HR (Imm/Def)	0.26 (95%CI: 0.11 to 0.64,	

	Immediate ART	Deferred ART
No. with event	8	16
HR (Imm/Def)	0.49 (95%CI: 0.21 to 1.15,	

INSIGHT START Study Group N Engl J Med 2015;373:795-807.

IMPLICATIONS OF START FOR CANCER

Immediate ART initiation significantly reduces risk of infection-related cancer during HIV infection

- Benefit of immediate ART not solely attributable to HIV RNA suppression
- May also be mediated by other mechanisms, such as a curb on oncogenic virus co-infection and reduction of inflammation.

Suggests immunity and inflammation are playing a significant role in cancer risk even at “near normal” CD4 counts

- Possible unrecognised immune defects
- Further research is needed to identify mediators of the benefit of immediate ART initiation in reducing risk of cancer and other comorbidities.

ADDITIONAL PREVENTION APPROACHES

Smoking cessation

- Elevated risk of lung cancer
- Above population level smoking rates
- Some risk likely directly attributable to HIV

Sun exposure

- Elevated risk of non-melanomatous skin cancer

Metabolic risk factors

- Likely to increase in importance with age

Vaccination

- Hepatitis B
- Human papillomavirus (?target groups)

SCREENING APPROACHES

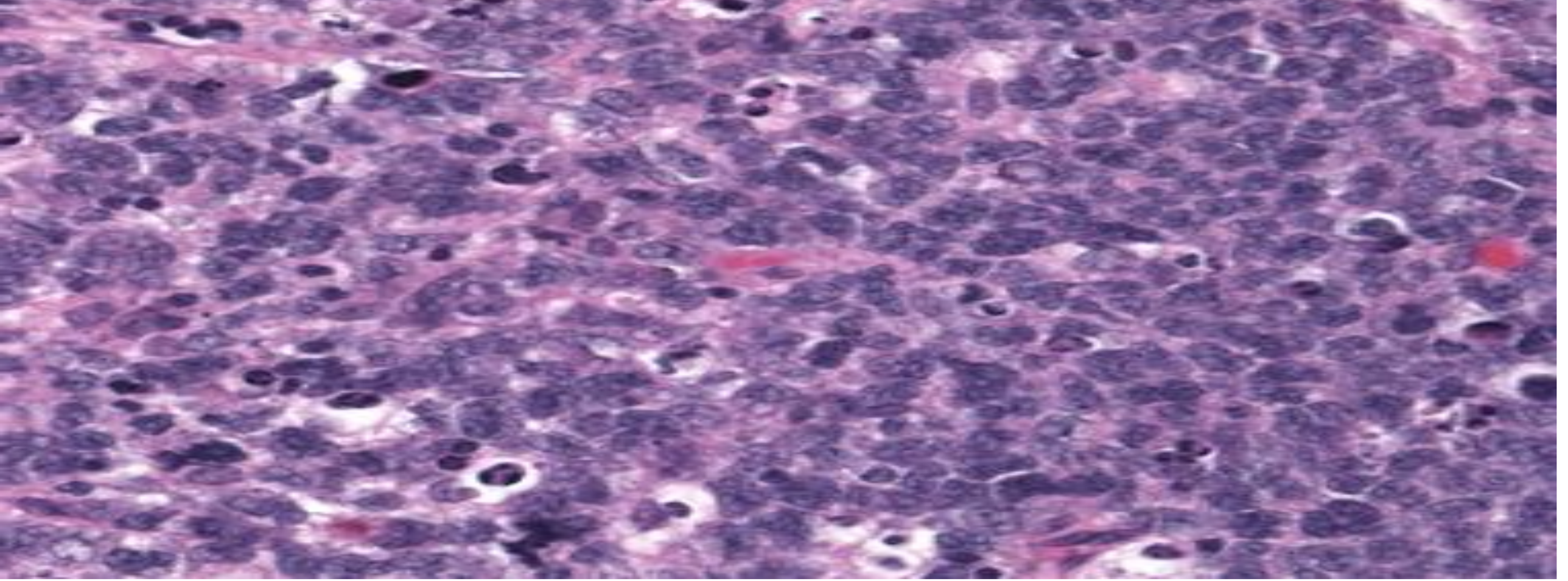
Standard population screening

- Evidence this may be less complete in people with HIV despite elevated risk – vertical care pathways

Specific screening approaches

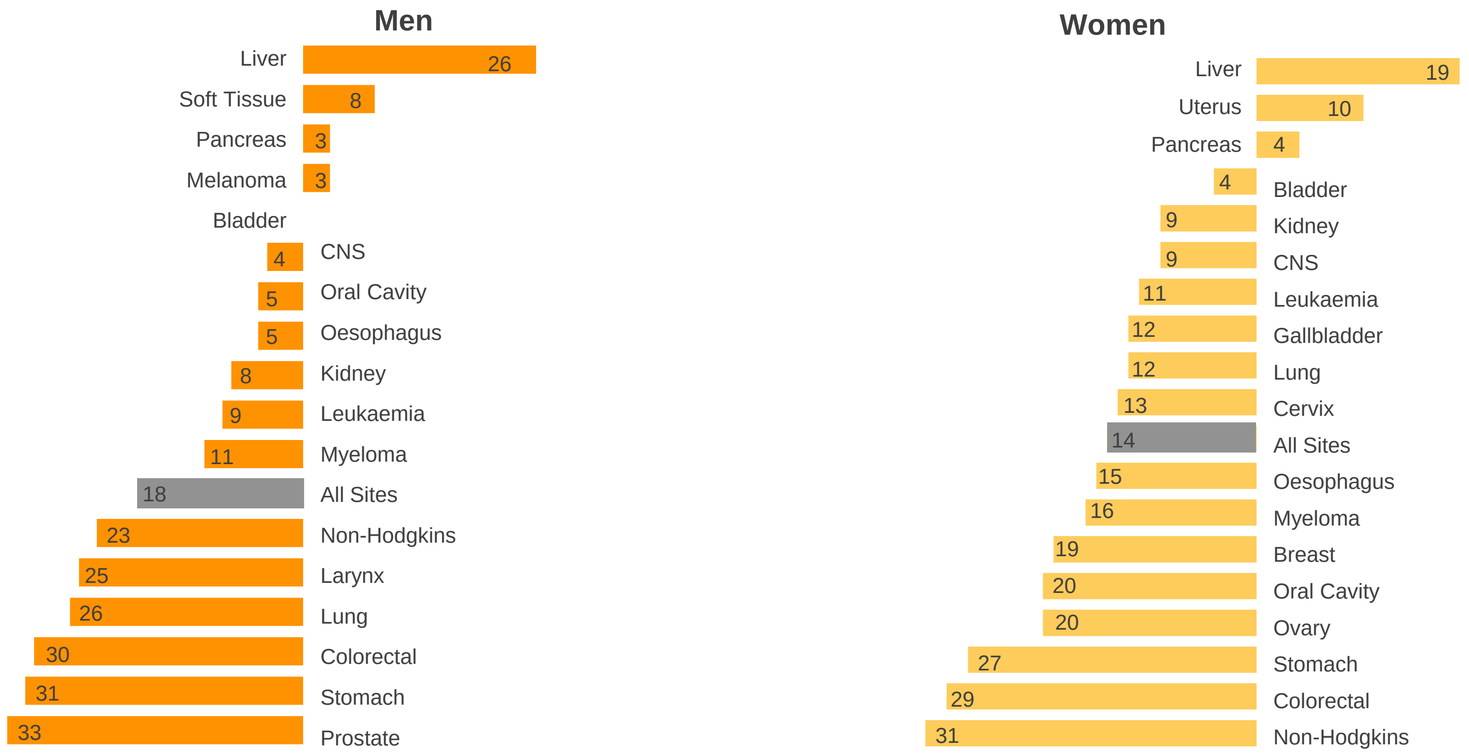
- Lung cancer
  Low dose CT for lung cancer – under investigation in US in HIV, not standard practice
- Anal cancer
  Anoscopy, cytology, other techniques all under investigation
- Haematological malignancies
  Immune activation markers and genetic markers under investigations

Role for identifying and targeting high risk populations within optimally treated HIV populations remains to be explored



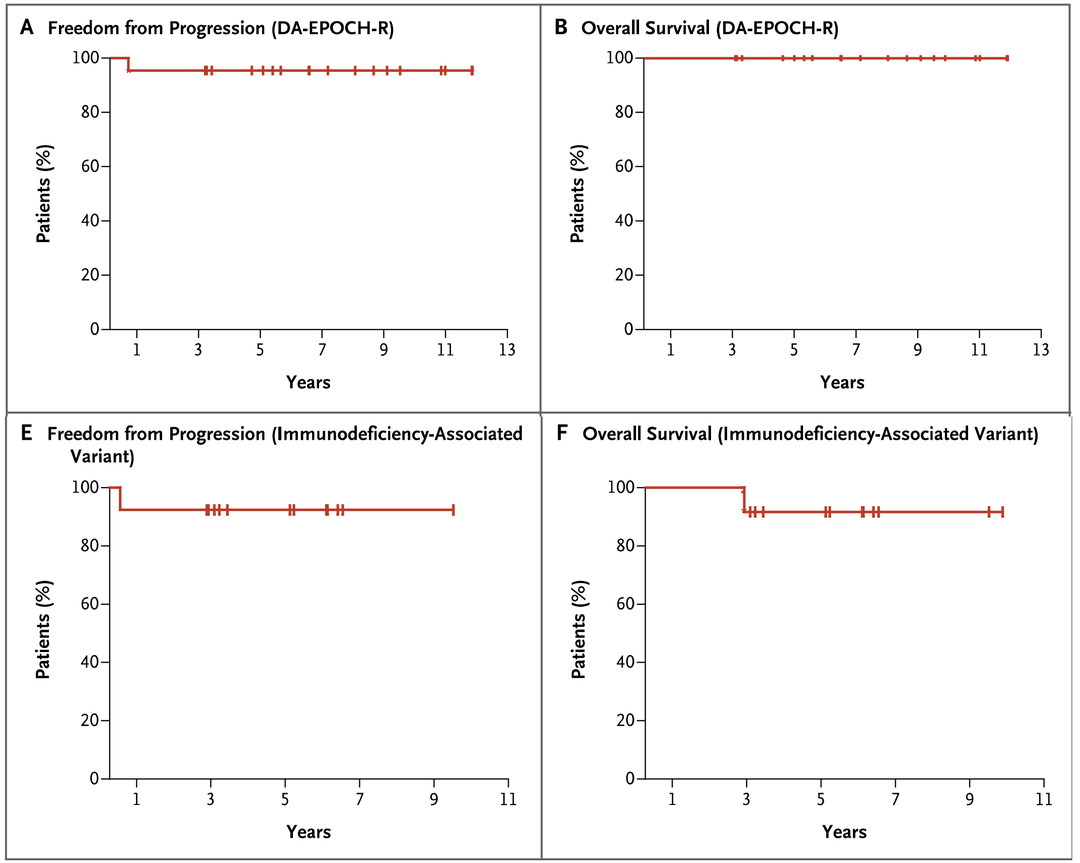
TREATMENT

CHANGING CANCER MORTALITY IN GENERAL POPULATION



U.S.National Cancer Institute Report to the Nation, 2015

HIV INFECTION AND CANCER OUTCOMES: BURKITT LYMPHOMA



Dunleavy K, et al. N Eng J Med 2013;369:1915- 25

HODGKIN LYMPHOMA IN HIV

	Primary Author	N	HAART era?	Stage III/IV	RR	CR	OS
EBVP	Errante	35	✗/✔	83	91	74	16m
VEBEP	Spina	71	✔	70	78	67	69% *(24m)*
ABVD*	Levine/ Gastaldi/Xicoy	21/ 8/62	✗/✔	75-100	62-100	43-100	76% *(60m)*
Stanford V	Spina	59	✗	71	89	81	59% *(60m)*
BEACOPP	Hartmann	12	✔	92	100	100	75% *(36m)*

Errante D, et al. Ann Oncol 1999;10:189-95. Spina M, et al. Ann Oncol 2008; 19(iv152, abstract no. 227). Levine AM, et al. JAIDS 2000;24:444-50. Gastaldi R, et al. Ann Oncol 2002;13:1158-60. Xicoy B, et al. Haematologica 2007;92:191-8. Spina M, et al. Blood 2002;100:1984-8. Hatrman P, et al. Ann Oncol 2003;14:1562-9.

DLBCL THERAPY IN HIV

	Primary Author	N	HAART era?	RR %	CR %	OS
CHOP	Vaccher	104 (80/24)	✗ ✔	-	36 50	50% at 0.5y 50% at 1.5y
CDE-R	Spina	74	✔	75	70	64% (2y)
CHOP-R	Kaplan	149	✔	65	58	50% (2.5y)
EPOCH-R	Sparano	48	✔	88	55-73	65% (2.5y)
EPOCH-RR	Dunleavy	33	✔	94	91	68% (5y)

Vaccher E, et al. Cancer 2001;91:155-63. Spina M, et al. Blood 2005;105:1891–1897. Kaplan LD, et al. Blood. 2005;106:1538–1543. Sparano JA, Blood. 2010 Apr 15; 115(15): 3008–3016.. Dunleavy K, et al. Blood. 2010;115:3017–3024.

HIV INFECTION AND CANCER OUTCOMES

Population studies suggest HIV positive people with cancer have worse overall survival and cancer-specific survival compared to uninfected people

Factors implicated in these outcomes

- Biologically aggressive disease
- More advanced stage at diagnosis
- Decreased immune surveillance
- Increased infective and immune-related complications

However in clinical trials outcomes in many malignancies, outcomes for people with HIV approach those in the uninfected population

What other factors are affecting outcomes in malignancy in people with HIV?

HIV INFECTION AND CANCER OUTCOMES

Cancer Type	Uninfected Cases without Treatment, N (%)	HIV-Infected Cases without Treatment, N (%)	Adjusted Odds Ratio (95%CI)*
DLBCL	5,157 (23.40)	207 (23.03)	1.39 (1.17, 1.65)
Cervix	1585 (8.55)	14 (12.73)	1.46 (0.79, 2.69)
Lung	53,323 (24.05)	181 (34.94)	1.55 (1.28, 1.87)
Anus	481 (8.05)	38 (8.28)	0.88 (0.59, 1.30)
Hodgkin lymphoma	1,839 (20.19)	75 (29.30)	1.68 (1.26, 2.24)
Prostate	52,579 (20.77)	63 (30.58)	1.48 (1.08, 2.02)
Colorectum	12,868 (7.22)	23 (14.74)	1.89 (1.15, 3.09)
Breast	12,067 (4.68)	9 (9.00)	1.60 (0.77, 3.34)

Suneja, G. et al JCO 2014

HIV INFECTION AND CANCER OUTCOMES

Local Stage Cancers:

Cancer Type	Standard Treatment Modality[a]	Adjusted Odds Ratio (95%CI)[b]
DLBCL	Chemotherapy	2.02 (1.50, 2.72)
Cervix	Surgery or radiotherapy	1.30 (0.39, 4.29)
NSCLC	Surgery or radiotherapy	2.43 (1.46, 4.03)
Colon	Surgery	4.77 (1.76, 12.96)
Breast	Surgery	1.38 (0.58, 3.29)

- **Predictors of Lack of Treatment (all stages):**
  - Low CD4 count
  - Male gender with IV drug use as mode of HIV exposure
  - Older age
  - Non-Hispanic Black race
  - Distant or unknown cancer stage
  - **Not** insurance status

Suneja, G. et al JCO 2014

ROLE OF ART

Role of HAART varies depending on tumor type:

Part of anti-tumor therapy in some cases (particularly viral malignancies): **KS, CNS lymphoma**

Improves outcomes by other mechanisms in others: anal cancer, perhaps cervical cancer

However not necessary immediately in all cases: often deferred in lymphoma therapy to avoid drug interactions

Newer antiretroviral agents have fewer interactions with drugs including chemotherapy

Consultation with ID and HIV pharmacy prior to chemotherapy (potentially including regimen changes)

Slide courtesy of presenter and represents the presenter's opinion

PREVENTING OI

Prevention of opportunistic infection and reactivation or progression of latent viral infections (herpes, hepatitis B and C, others)

Risk may persist depending on agents used, and late infections can be life threatening (post-rituximab)

Few prospective data to guide use of anti-infective agents

Where possible, maintain or commencement of HAART

Commonly adapt from general HIV guidelines:

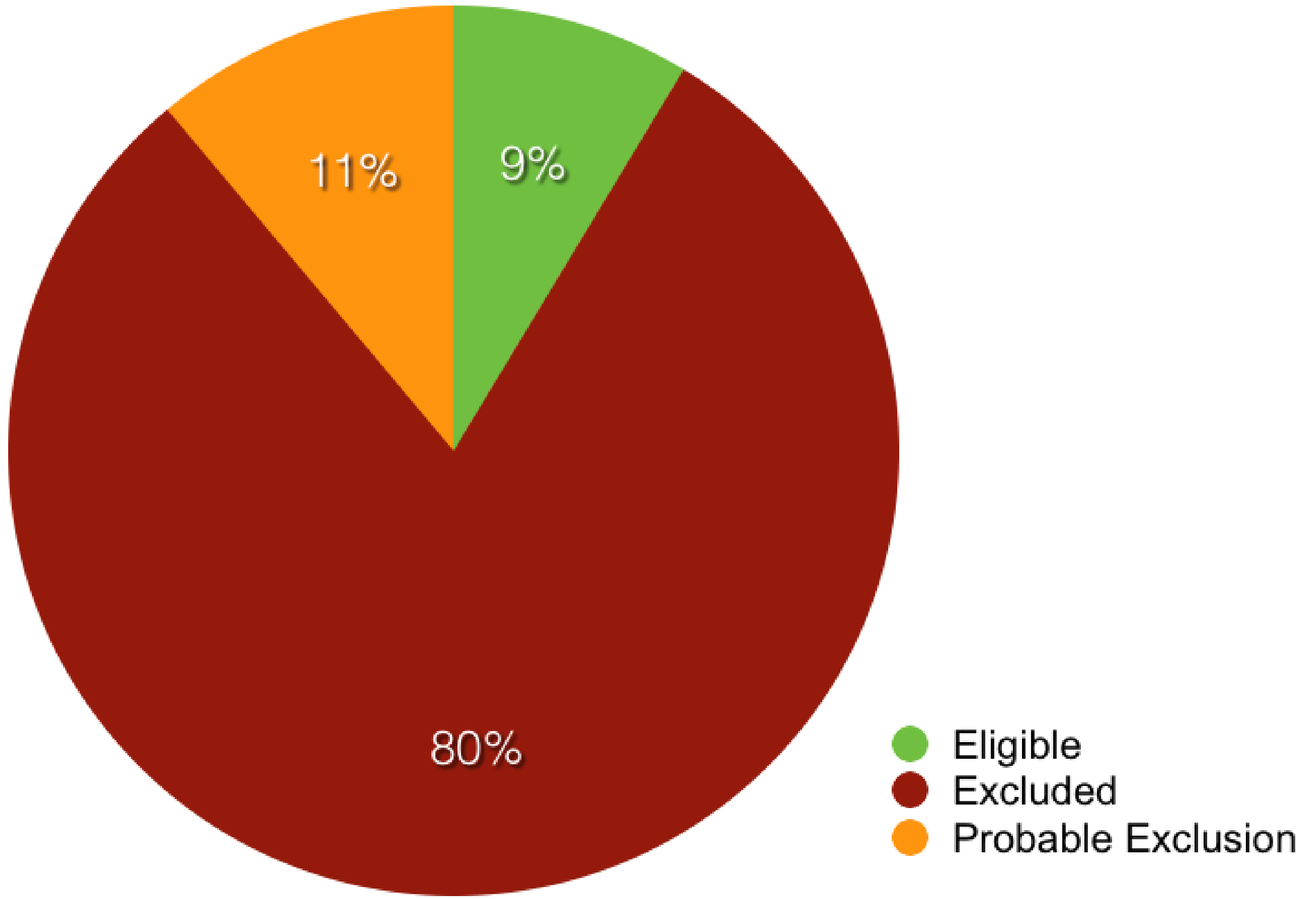
Herpes prophylaxis if relevant history

PCP prophylaxis if CD4<200 and MAC if <100

May continue prophylaxis past conventional thresholds until recovery

Slide courtesy of presenter and represents the presenter's opinion

CLINICAL TRIAL ACCESS



People with HIV are routinely excluded from trials of anti-cancer agents, despite the disproportionate burden of malignancy

Uldrick TS, et al J Clin Oncol 2017;35:3774-80

CLINICAL TRIAL ACCESS

Friends of ASCO Recommendations

Patients with CD4+ T-cell counts >350 cells/mL should generally be eligible

Lower CD4+ count eligibility is often appropriate

Patients with no history or remote history of AIDS-defining opportunistic infections should generally be eligible

For studies of AIDS-defining cancers with curative potential, exclusion limited to uncontrolled opportunistic infections may be appropriate

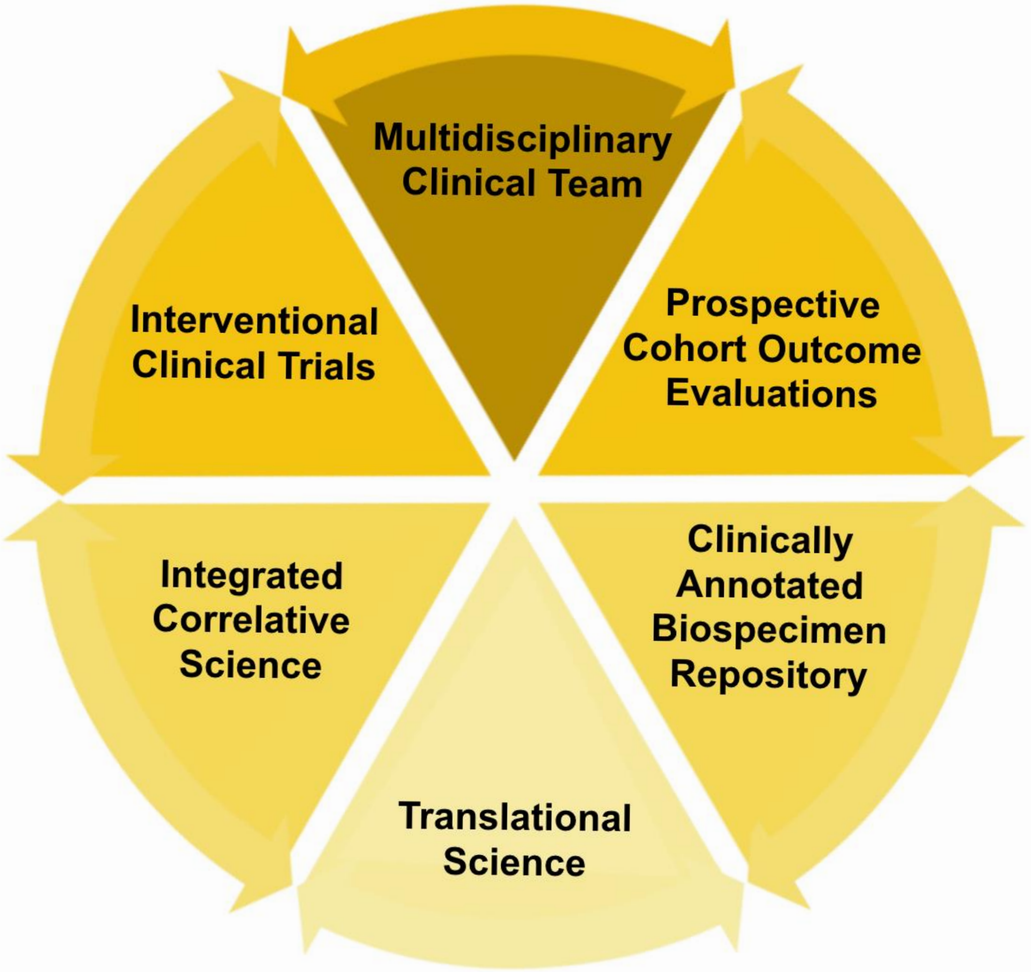
Patients on prophylactic antimicrobials need not be excluded, although specific agents may be excluded for interactions or toxicities.

Generally recommend concurrent treatment with effective ART according to current local treatment guidelines

Recommend exclusion of specific ART agents, when indicated

Uldrick TS, et al J Clin Oncol 2017;35:3774-80

INTEGRATED CLINICAL MODELS



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IMMUNE MODULATION IN KAPOSI SARCOMA

Emerging classes of agents targeting host immune response to cancer

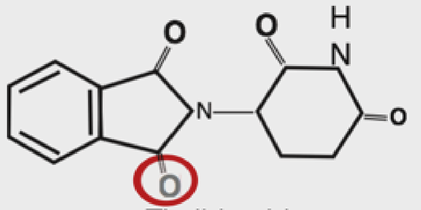
- Activity in a variety of solid and haematological tumours
- May be particularly useful in malignancy associated with infection and immune deficiency
- Responding to immune deficits underlying pathogenesis

Multiple classes

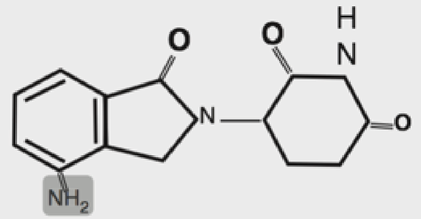
- Checkpoint inhibitors
- Immune modulatory thalidomide derivatives (IMID)

Pomalidomide

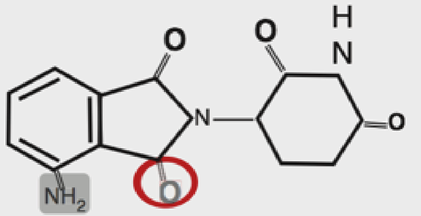
- Most potent current IMID
- Excreted renally and by hydrolysis
- No predicted interactions with ART



Thalidomide



Lenalidomide

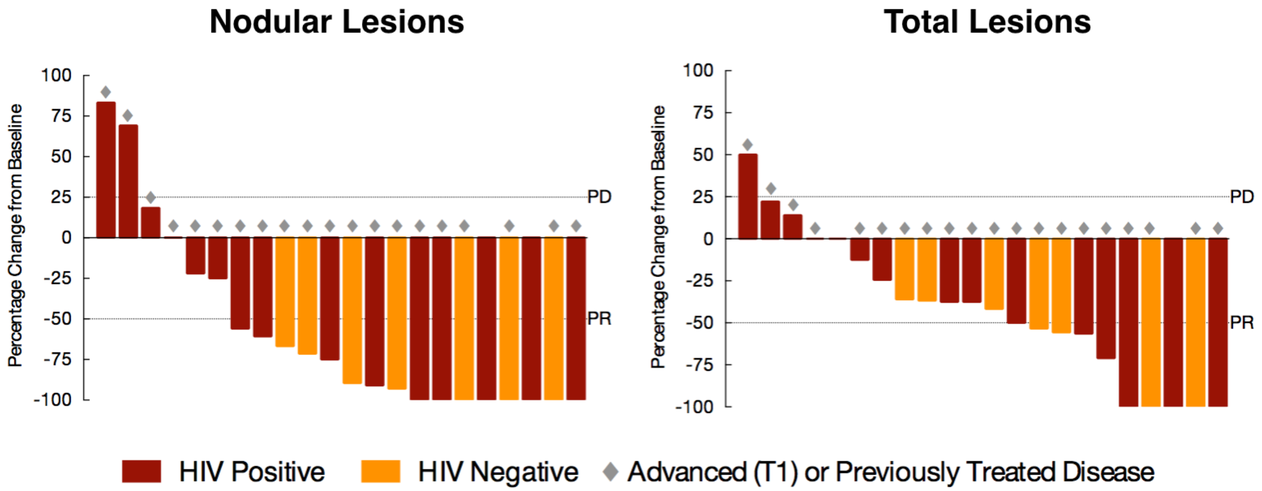


Pomalidomide

CLINICAL RESPONSES

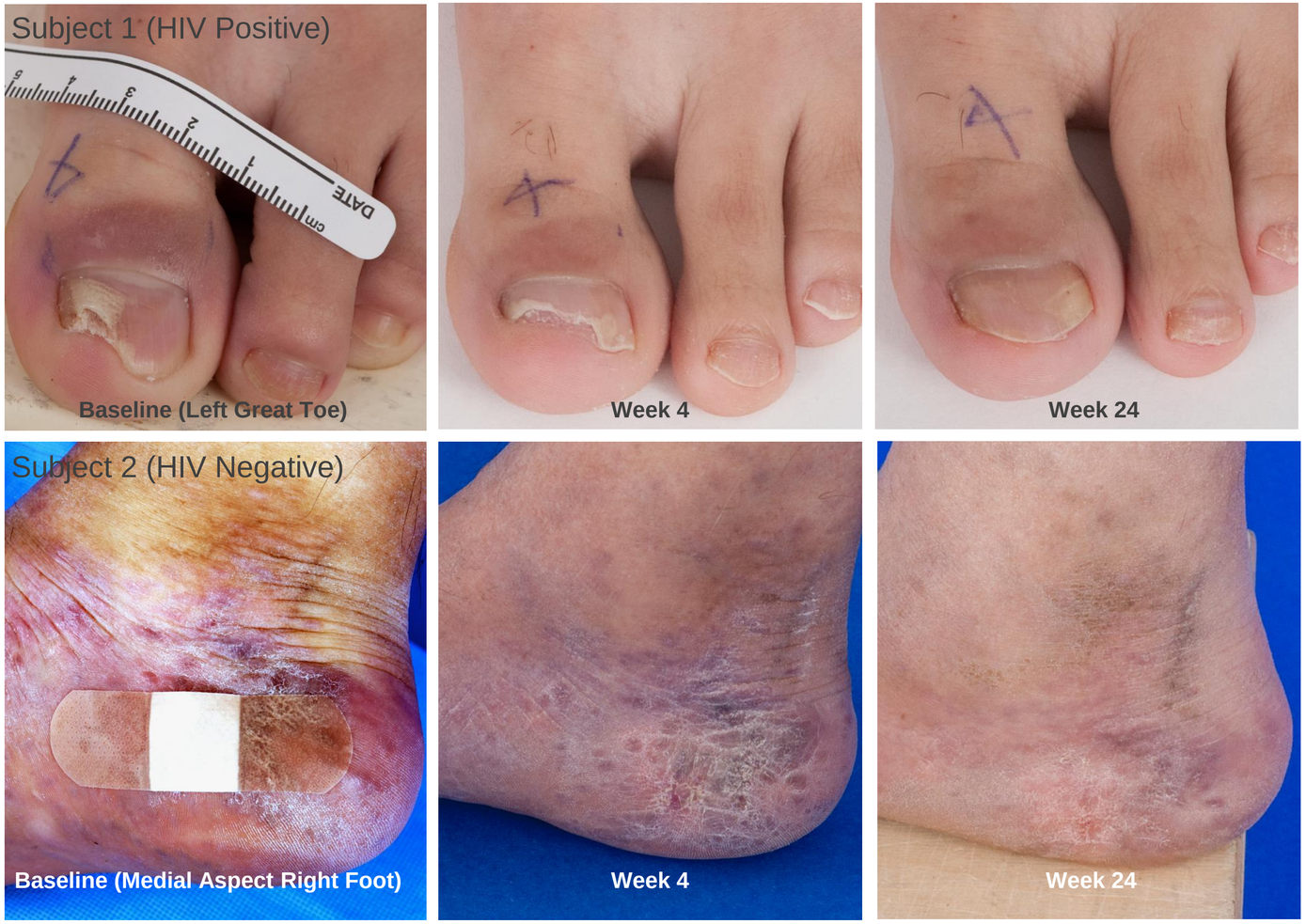
	Enrolled (Assessable)	Overall Response	Complete Response	Partial Response	Stable Disease	Progressive Disease	Time to Response
Combined	22 (22)	**16 (73%)**	4 (18%)	12 (55%)	3 (14%)	3 (14%)	**4 weeks (4–36**
HIV positive	15 (15)	**9 (60%)**	3 (20%)	6 (40%)	3 (20%)	3 (20%)*	**8 weeks (4–32**
HIV negative	7 (7)	**7 (100%)**	1 (14%)	6 (86%)	0	0	**4 weeks (4–36**

*Includes one subject who became non-adherent to ART and protocol therapy



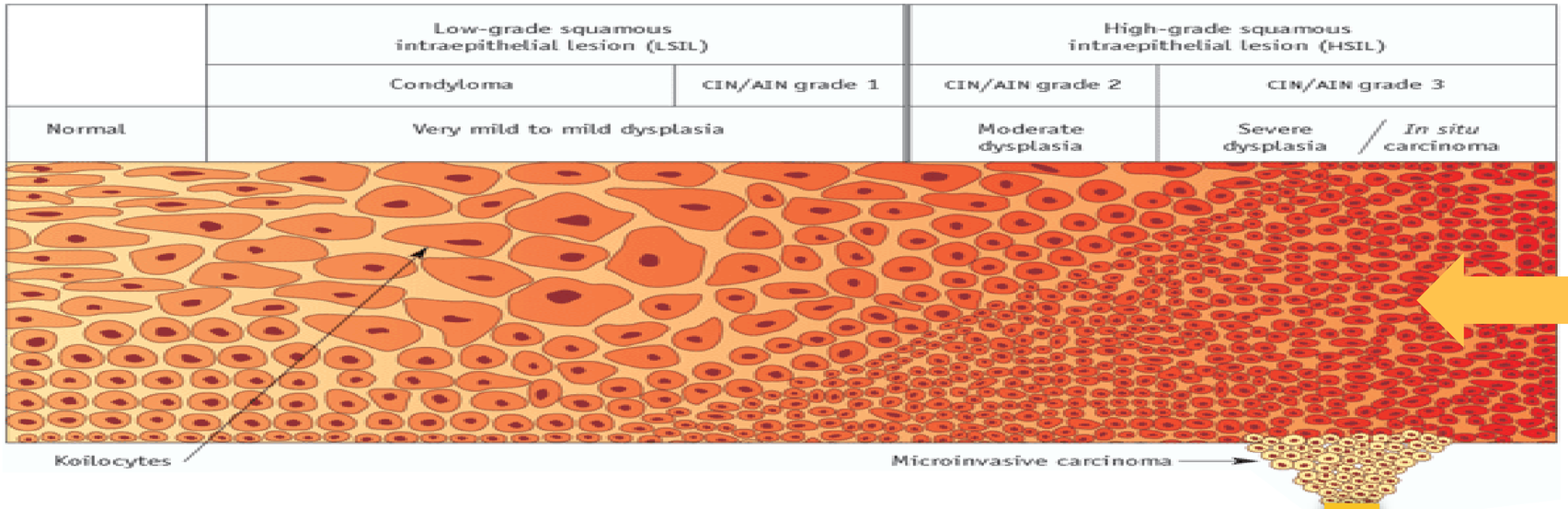
- Polizzotto, Journal of Clinical Oncology 2016

CLINICAL RESPONSES



- Polizzotto, Journal of Clinical Oncology 2016

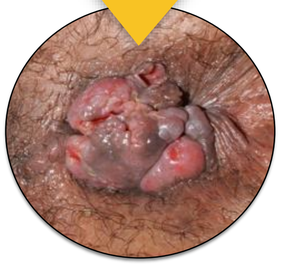
IMMUNE MODULATION IN OTHER VIRAL TUMOURS IN HIV



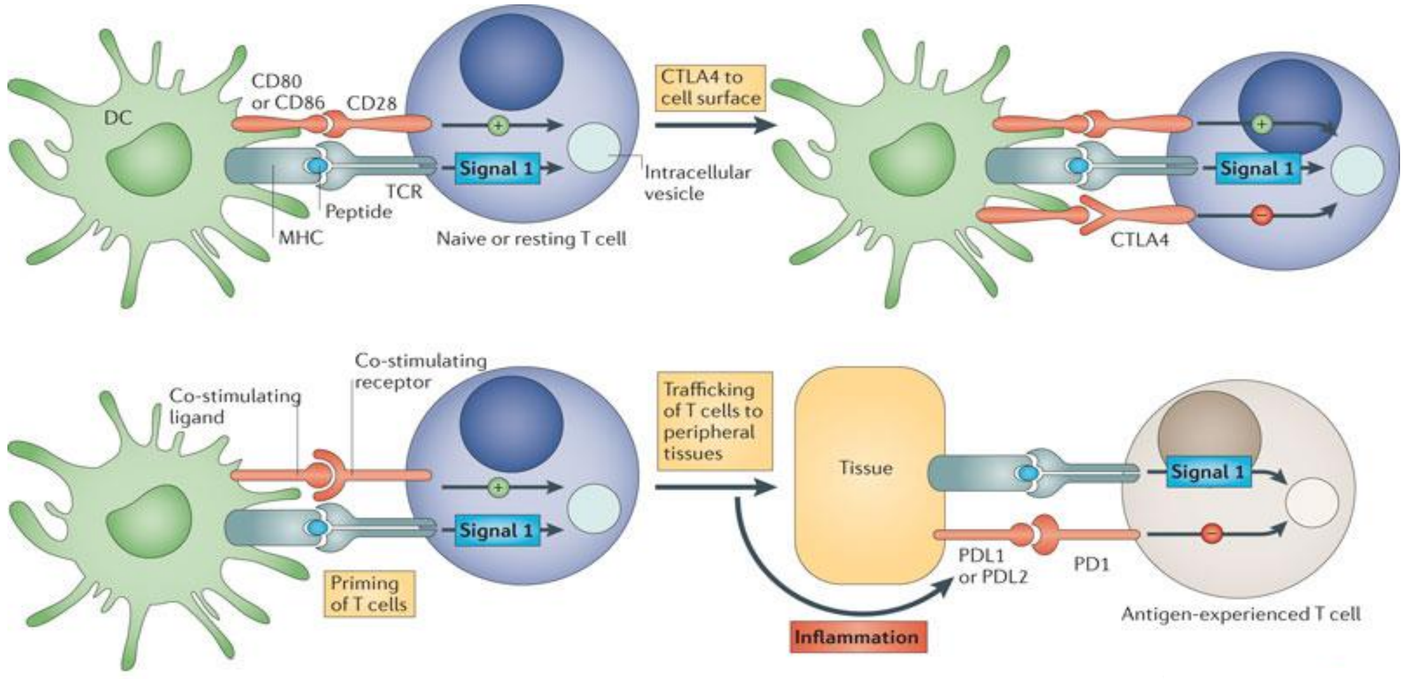
IMMUNE INTERVENTION (IN ADDITION TO ART): POMALIDOMIDE

- Natural history of anal dysplasia very poorly understood
- Existing evidence is that progression to cancer is less common than in the cervix
  - About 1/400 per year in HIV positive gay men
  - About 1/4000 per year in HIV negative gay men

<<1%/yr



IMMUNE CHECKPOINT INHIBITION IN HIV MALIGNANCIES



AMC-095

Post first line or unresectable including HL

Nivolumab ± Ipilimumab

Phase I/II

Standard ART

CD4>100 or >200 (stratified)

Available at: https://clinicaltrials.gov/ct2/show/NCT02408861 (accessed Sept. 2018).

Nivolumab in combination with ipilimumab is not TGA-registered for Hodgkin Disease. This combination has not been evaluated for safety or efficacy by the TGA for this indication

CONCLUSIONS

- Elevated risk of malignancy remains a defining feature of HIV infection
- Epidemiology of HIV-associated malignancies is evolving with reduction in severe immunosuppression
- Population ageing into time of greatest cancer risk
- Early initiation of ART is the most important intervention to prevent cancer, even at high CD4 counts
- Other interventions including smoking cessation are likely complementary
- With effective ART and immune reconstitution, standard therapies are deliverable with multi-disciplinary support
- Attention to drug-drug interactions and OI prevention required
- Better access to investigational cancer therapies is needed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