IeDEA data for cancer incidence and risk factors - challenges and limitations

Julia Bohlius, MD MScPH
IeDEA-Southern Africa
Co-chair IeDEA cancer working group

23 June 2016

Outline

- Cancer in HIV-positive populations
- Cancer epidemiology in HIV cohorts
- Analyses based on IeDEA data
- Probabilistic record linkages
- Limitations

CANCER IN HIV-POSITIVE POPULATIONS

THE NEW YORK TIMES,
FRIDAY, JULY 3, 1981

A20 L

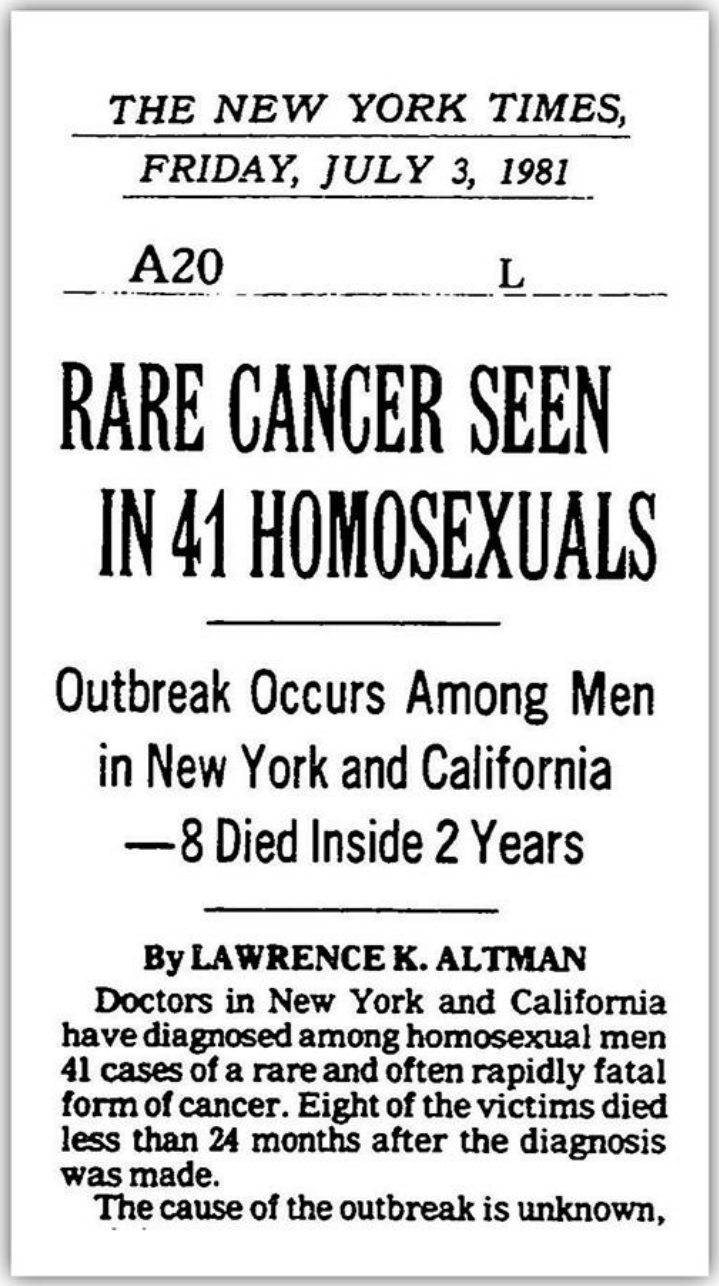
RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown,



THE NEW YORK TIMES,
FRIDAY, JULY 3, 1981

A20 L

RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

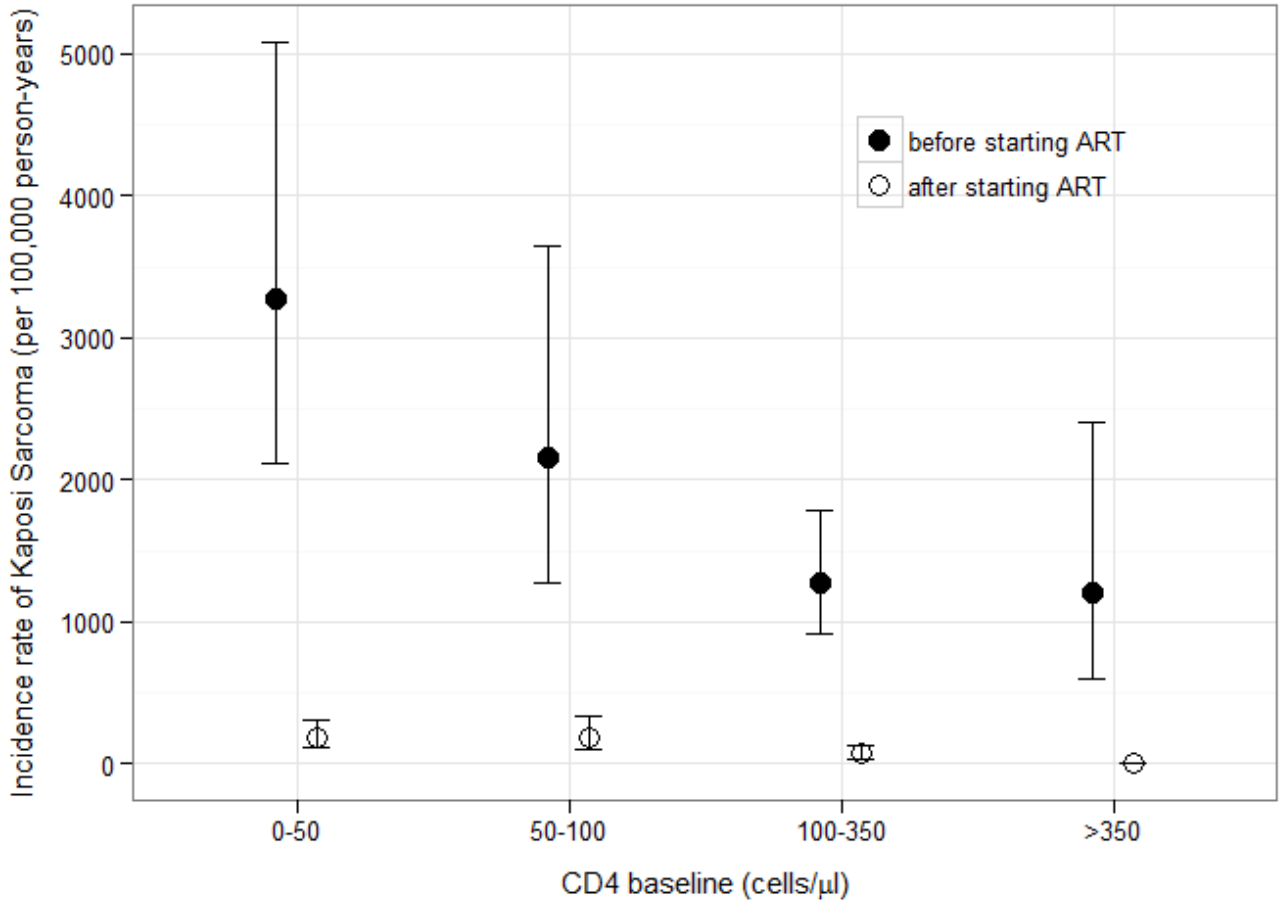
The cause of the outbreak is unknown,

Epidemic Kaposi Sarcoma

- Frequent
- Aggressive clinical course
- Young patients

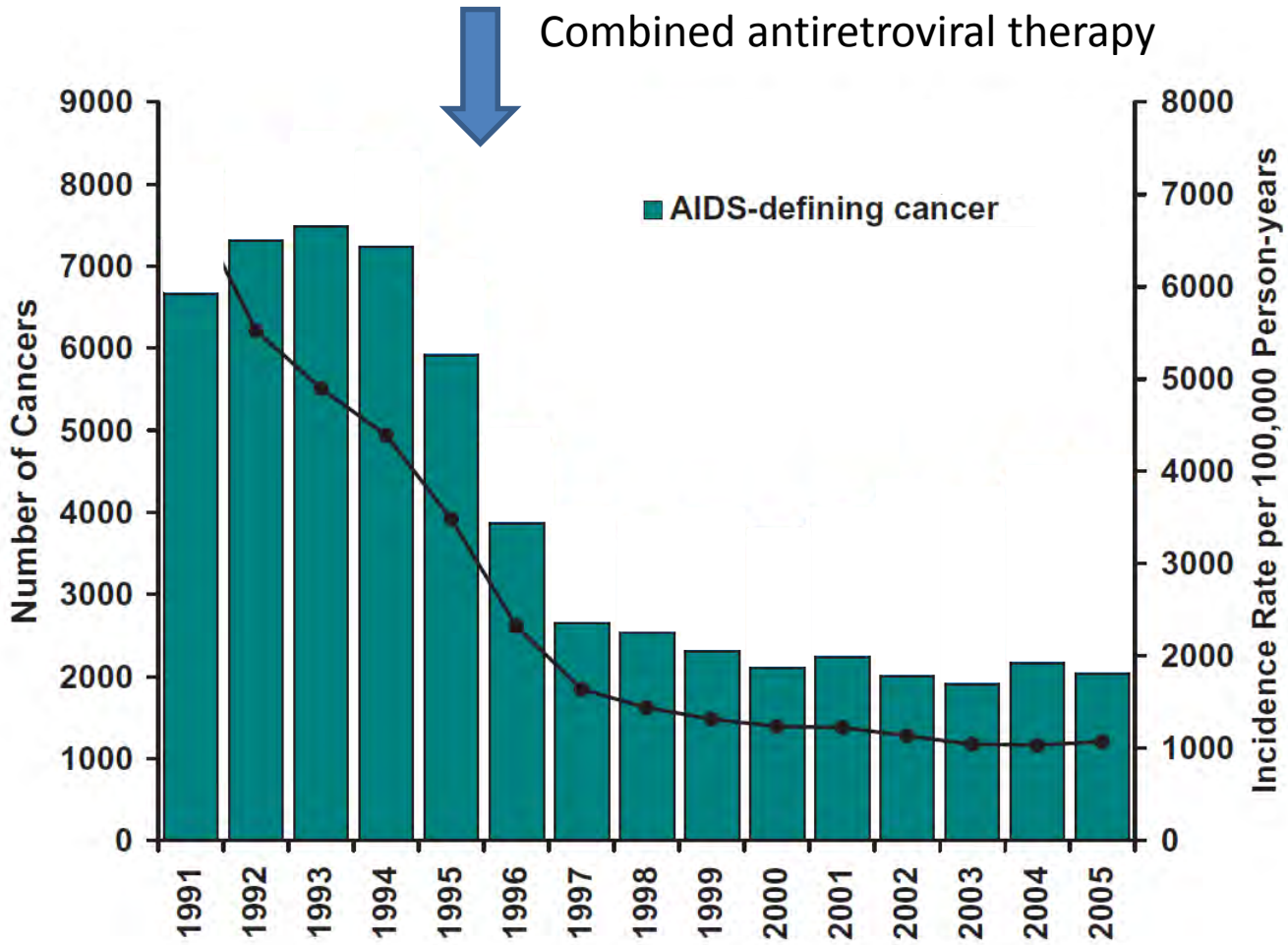
Kaposi sarcoma and immunodeficiency South Africa

Data from the IeDEA-SA collaboration



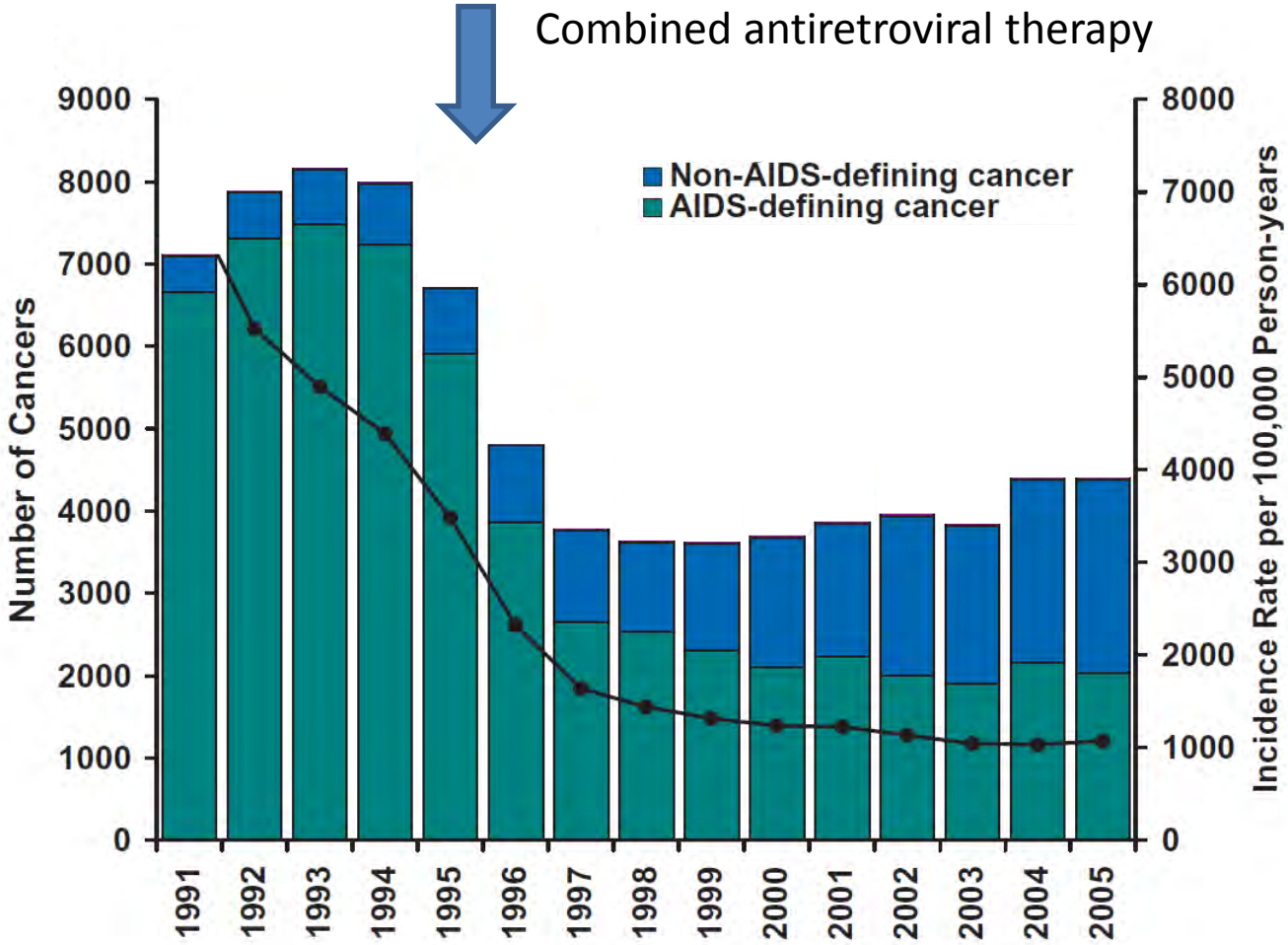
Bohlius et al , IJC 2014

AIDS-defining cancers USA



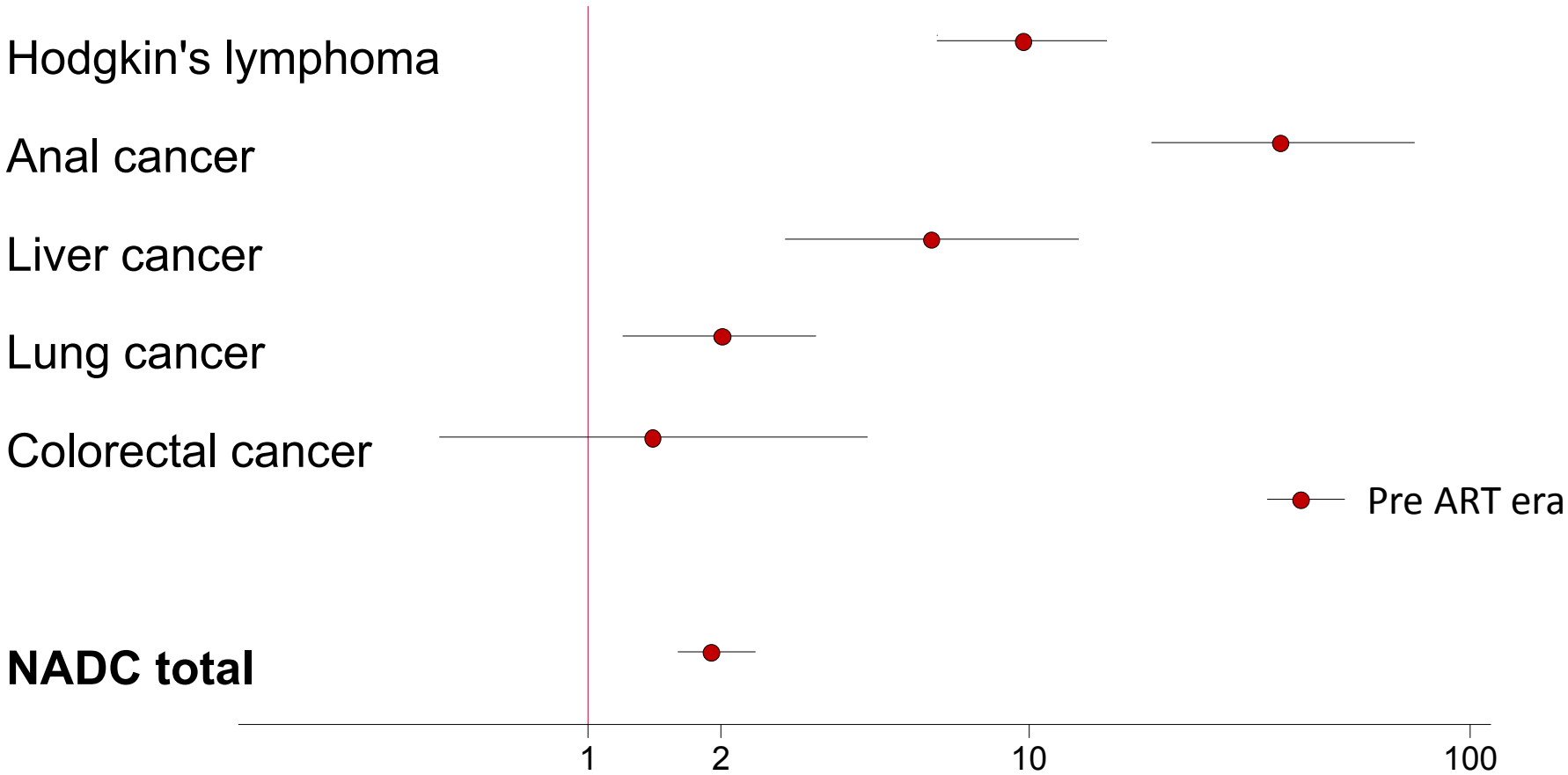
Adapted from Shiels et al, JNCI 2011

Non AIDS-defining cancers USA



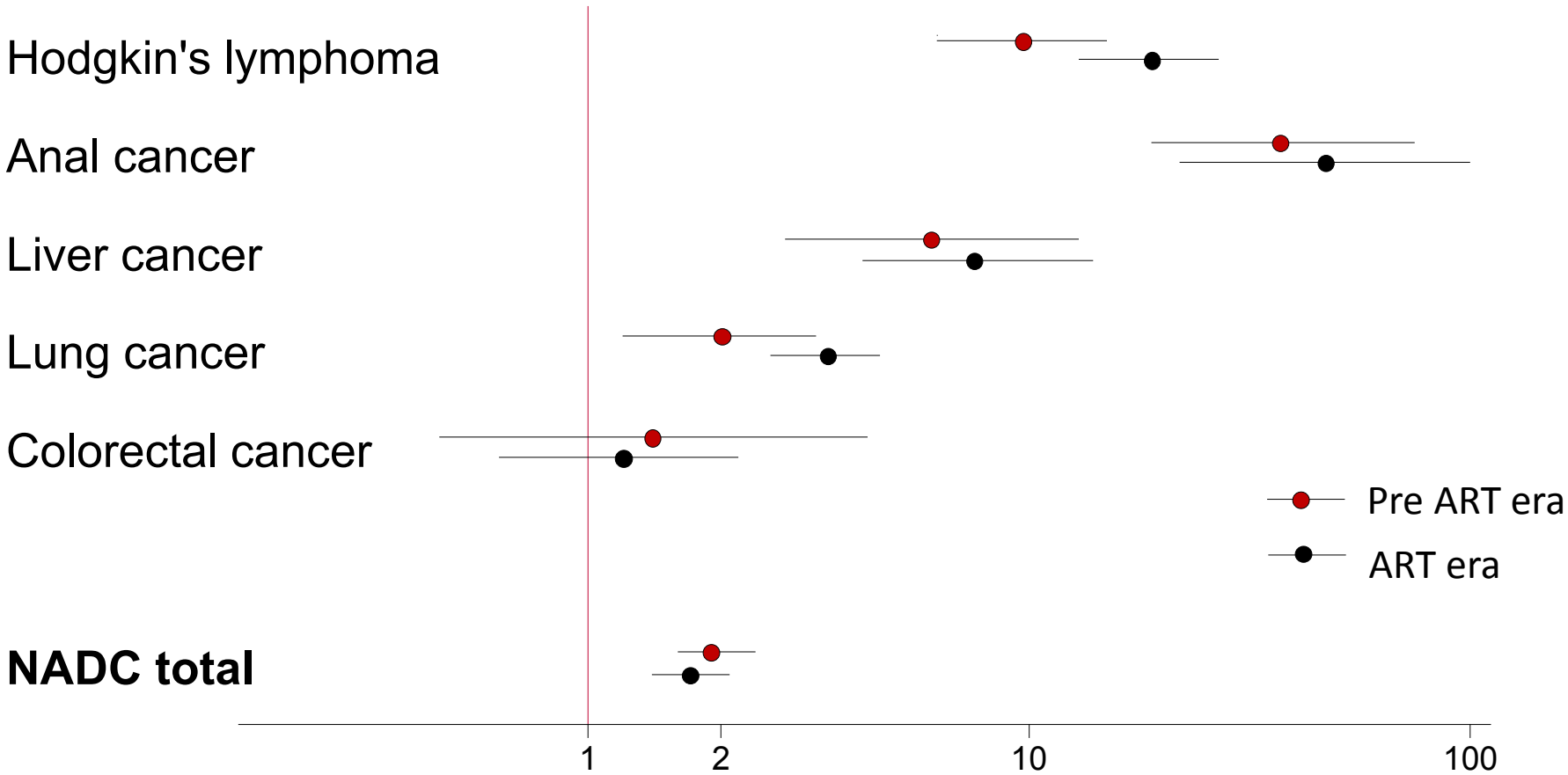
Adapted from Shiels et al, JNCI 2011

Standardised incidence ratios for non AIDS-defining cancers



Adapted from Shiels et al, JAIDS 2009

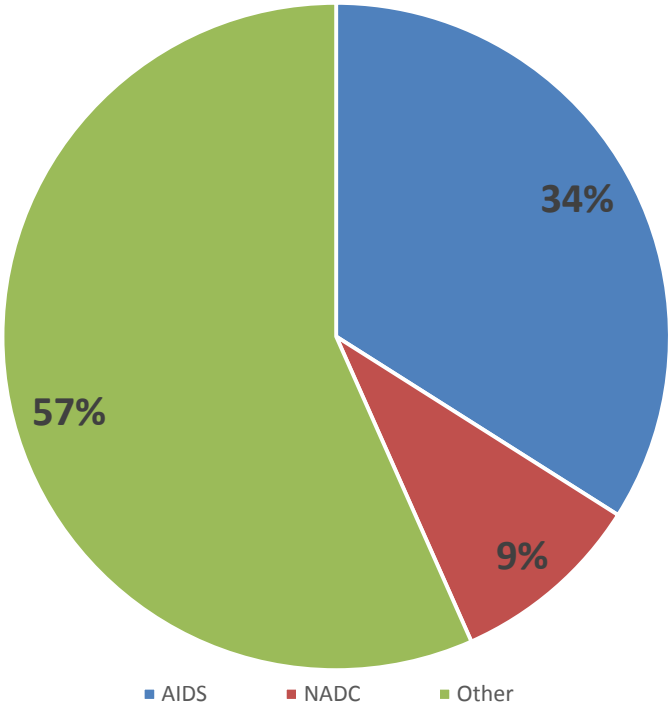
Standardised incidence ratios for non AIDS-defining cancers



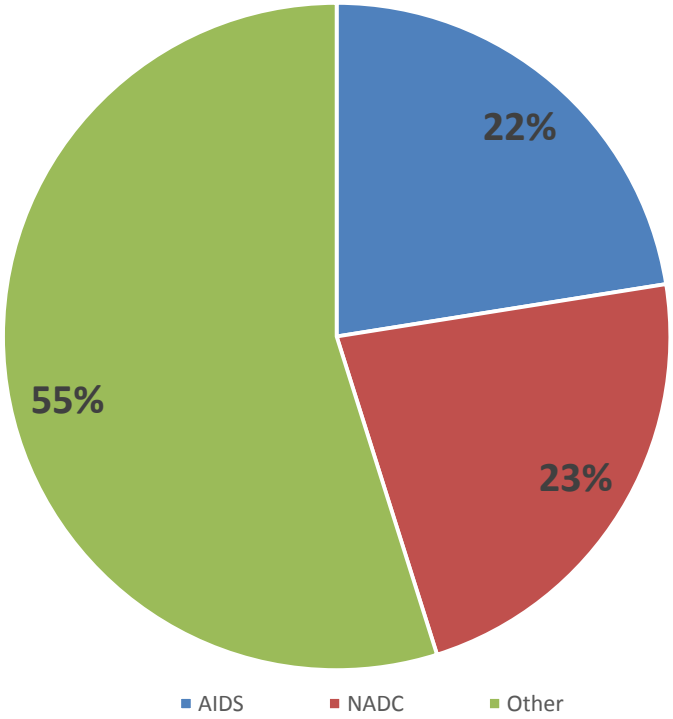
Adapted from Shiels et al, JAIDS 2009

Causes of deaths in HIV-positives Europe

1999-2000



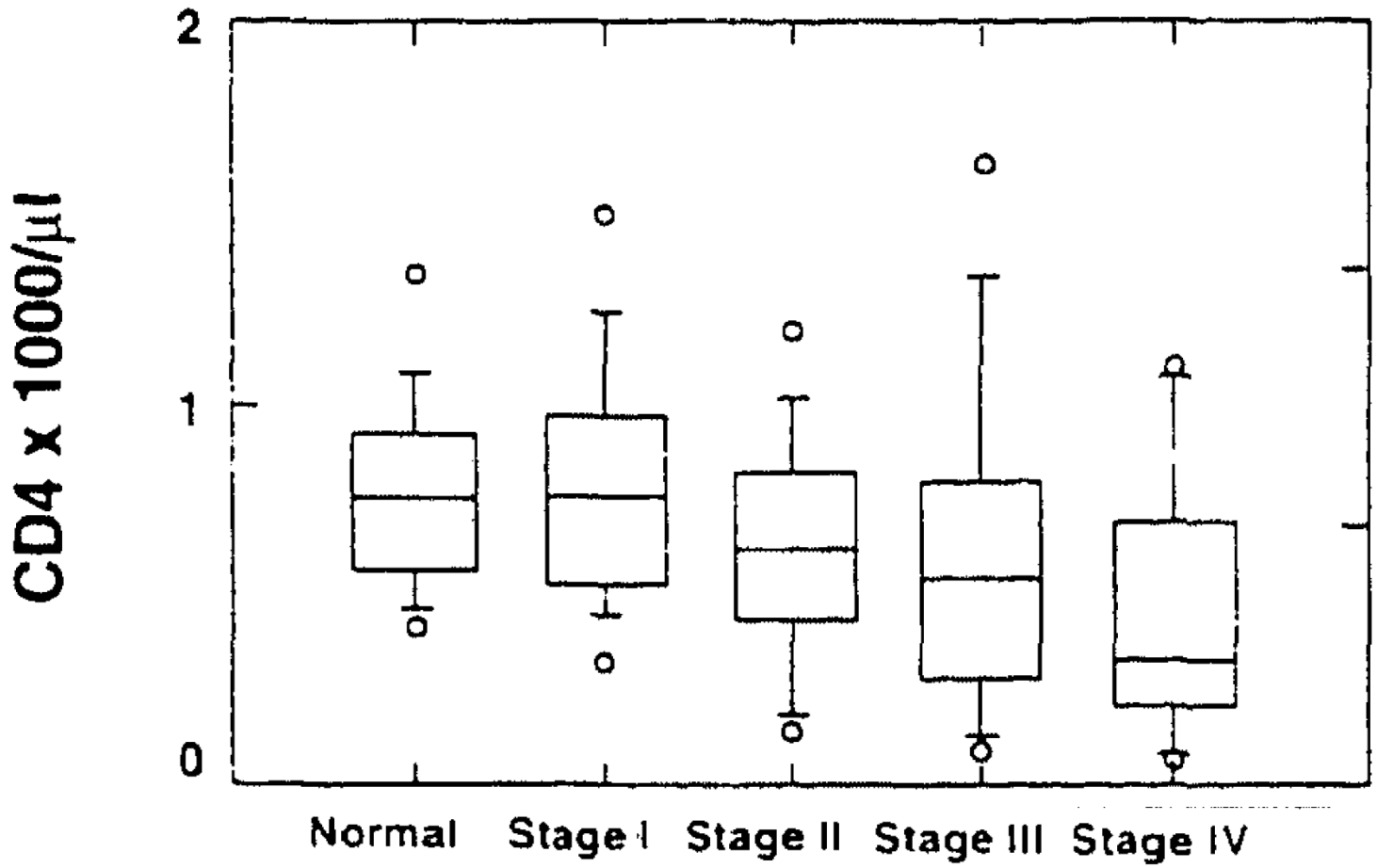
2009-2011



Adapted from Smith et al, Lancet 2014

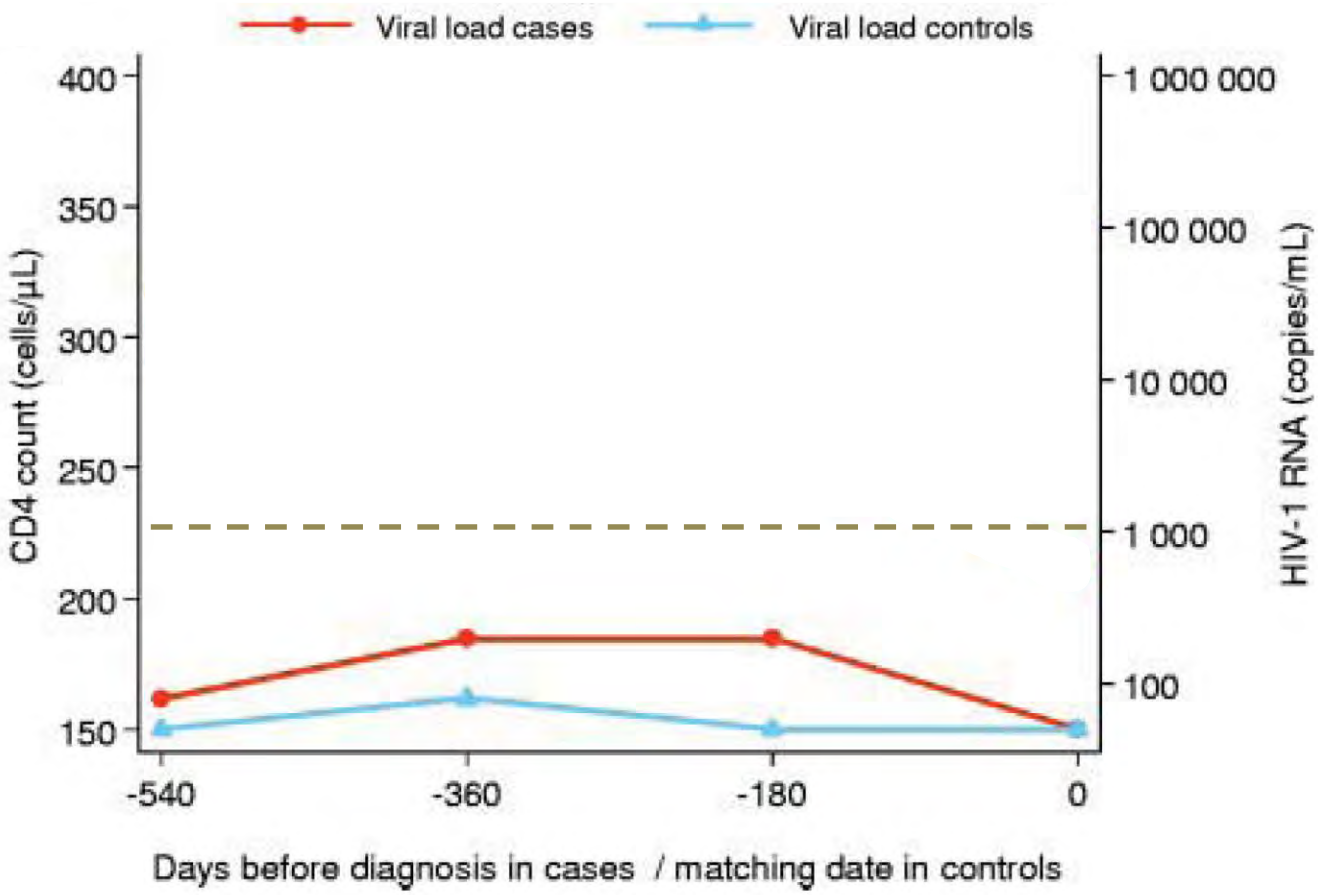
CANCER EPIDEMIOLOGY IN HIV COHORTS

Hodgkin's lymphoma in HIV negative patients

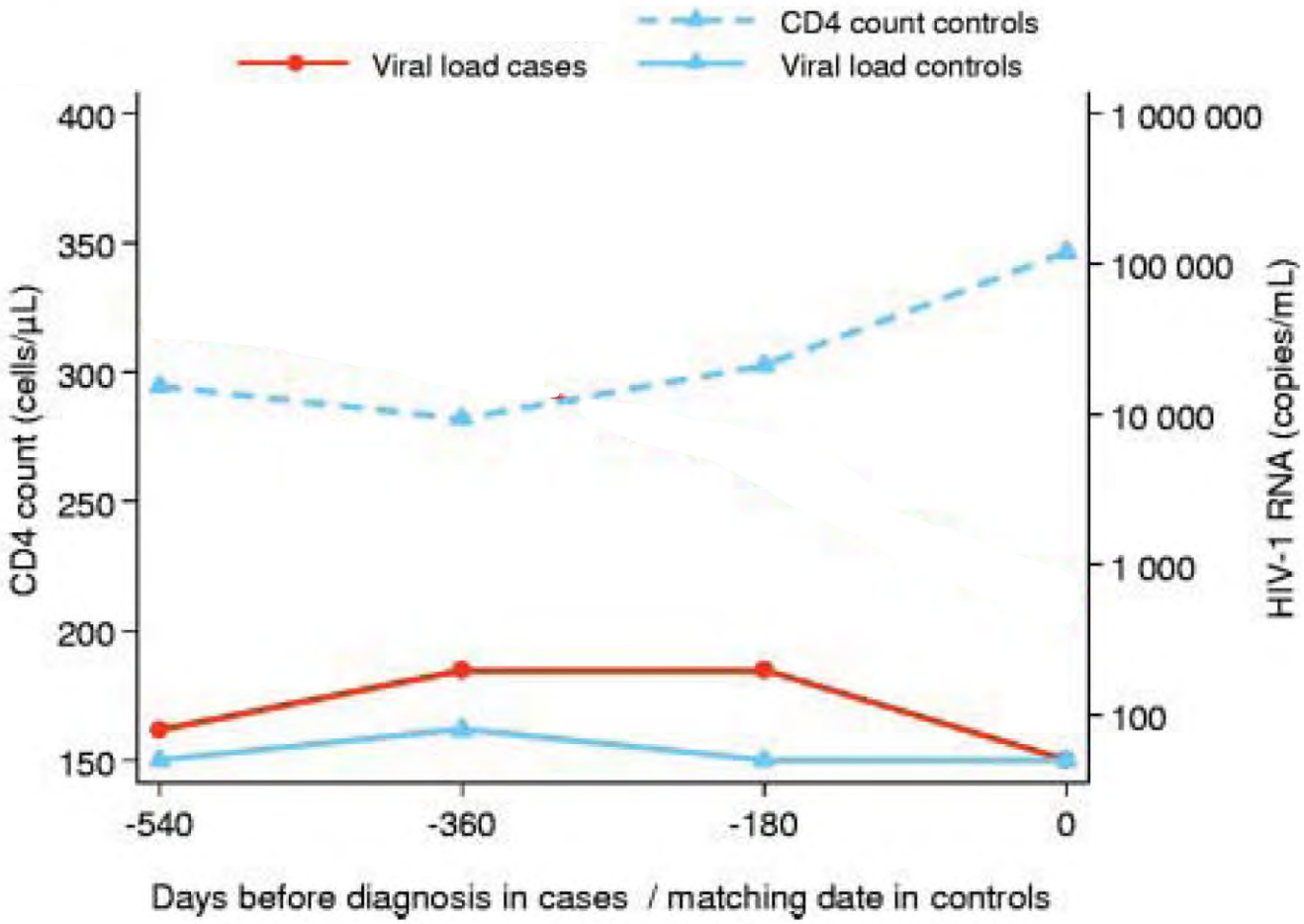


Ayoub et al 1999

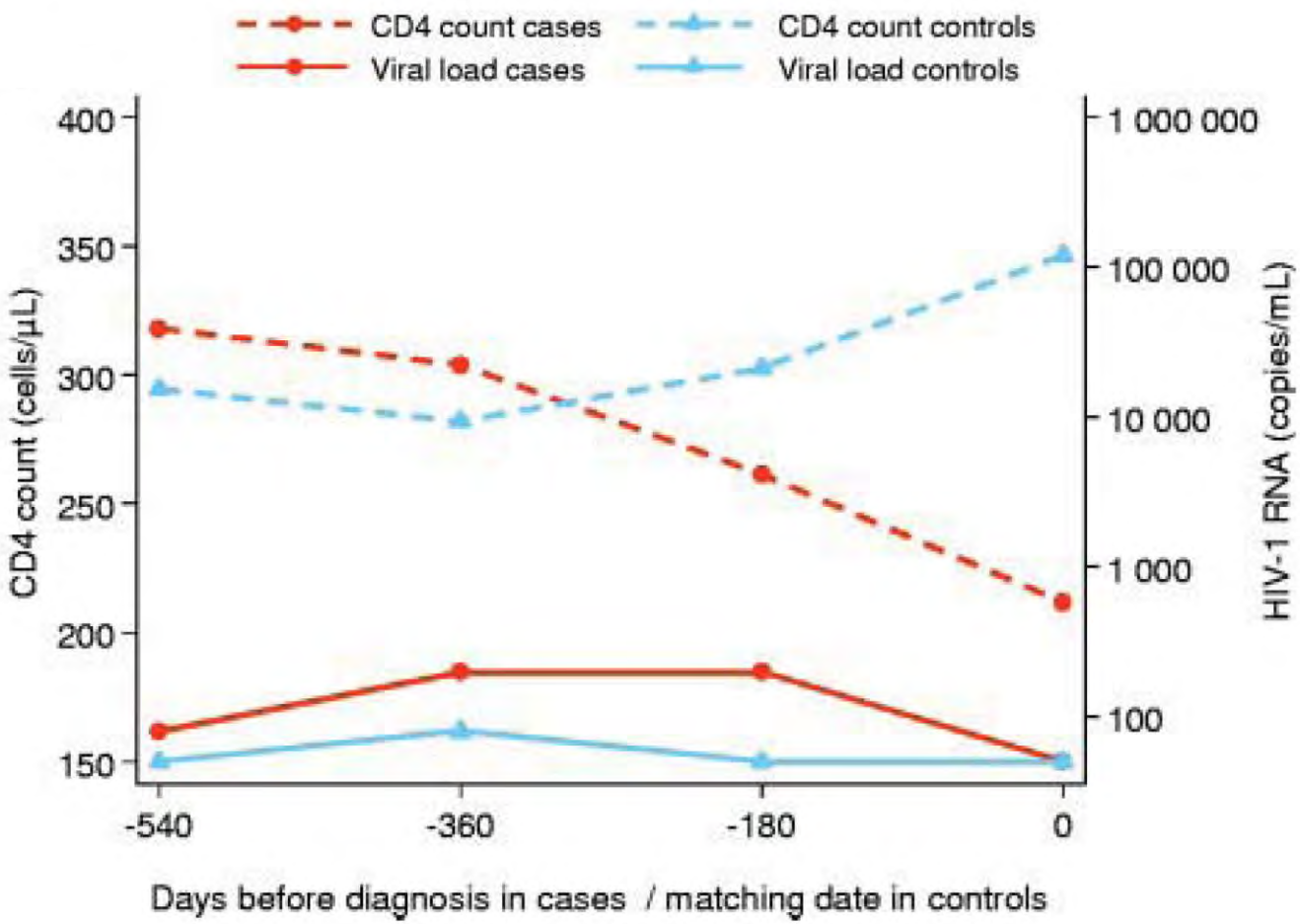
Hodgkin's lymphoma: evolution of CD4 cell counts



Hodgkin's lymphoma: evolution of CD4 cell counts



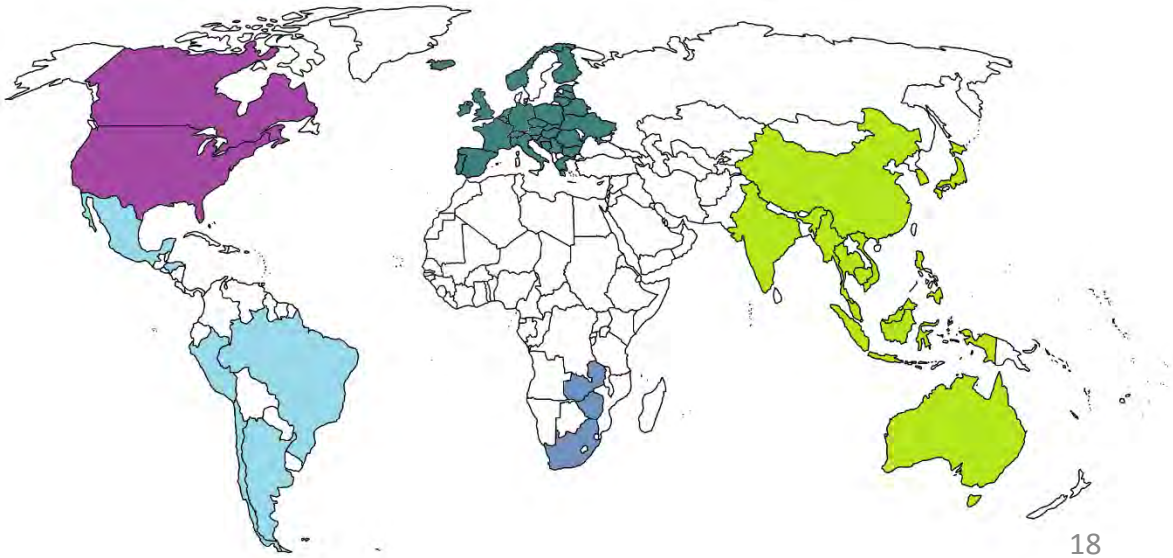
Hodgkin's lymphoma: evolution of CD4 cell counts



GLOBAL IEDEA ANALYSES

Objective

To estimate and compare incidence rates and risk factors for developing AIDS defining cancers in HIV-positive persons who initiated combination antiretroviral therapy (ART) across geographic regions



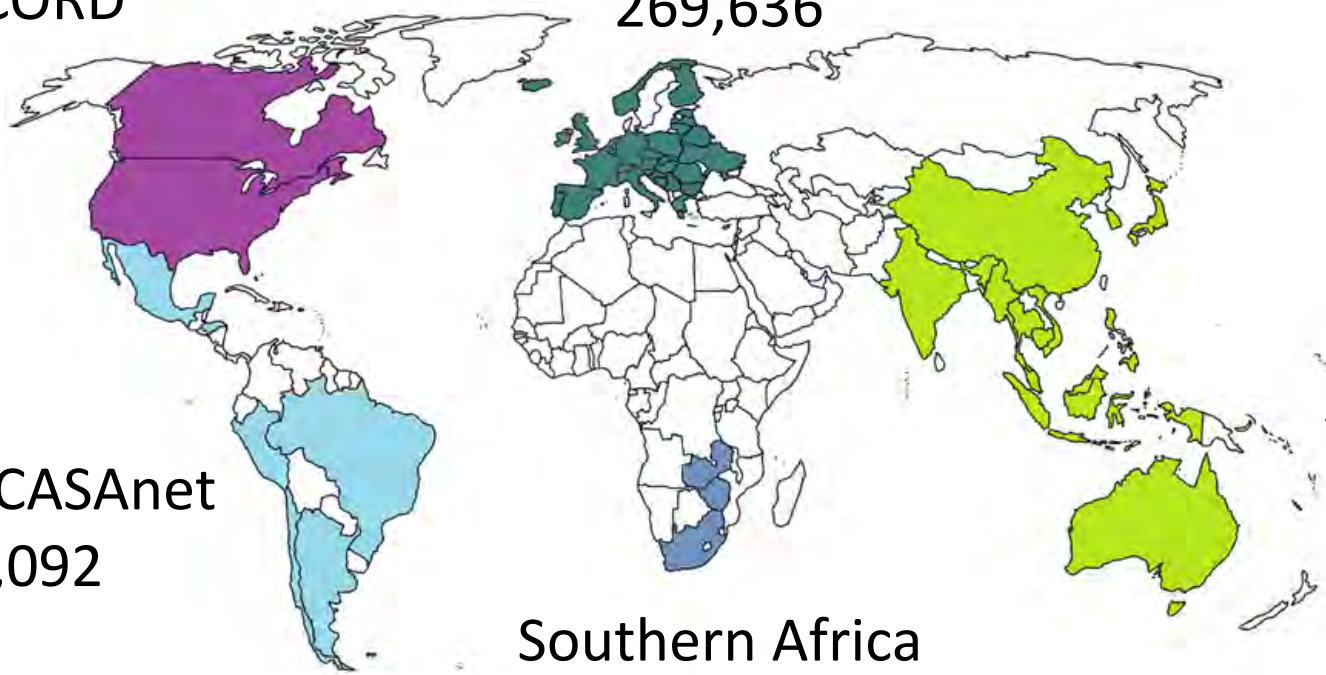
Databases

International collaborations of observational HIV cohorts:

1. International Epidemiologic Databases to Evaluate AIDS IeDEA
   - Asia-Pacific
   - Southern Africa
   - CCASAnet (Latin America)
   - NA-ACCORD (North America)

2. Collaboration of Observational HIV Epidemiological Research in Europe COHERE in EuroCoord

Databases

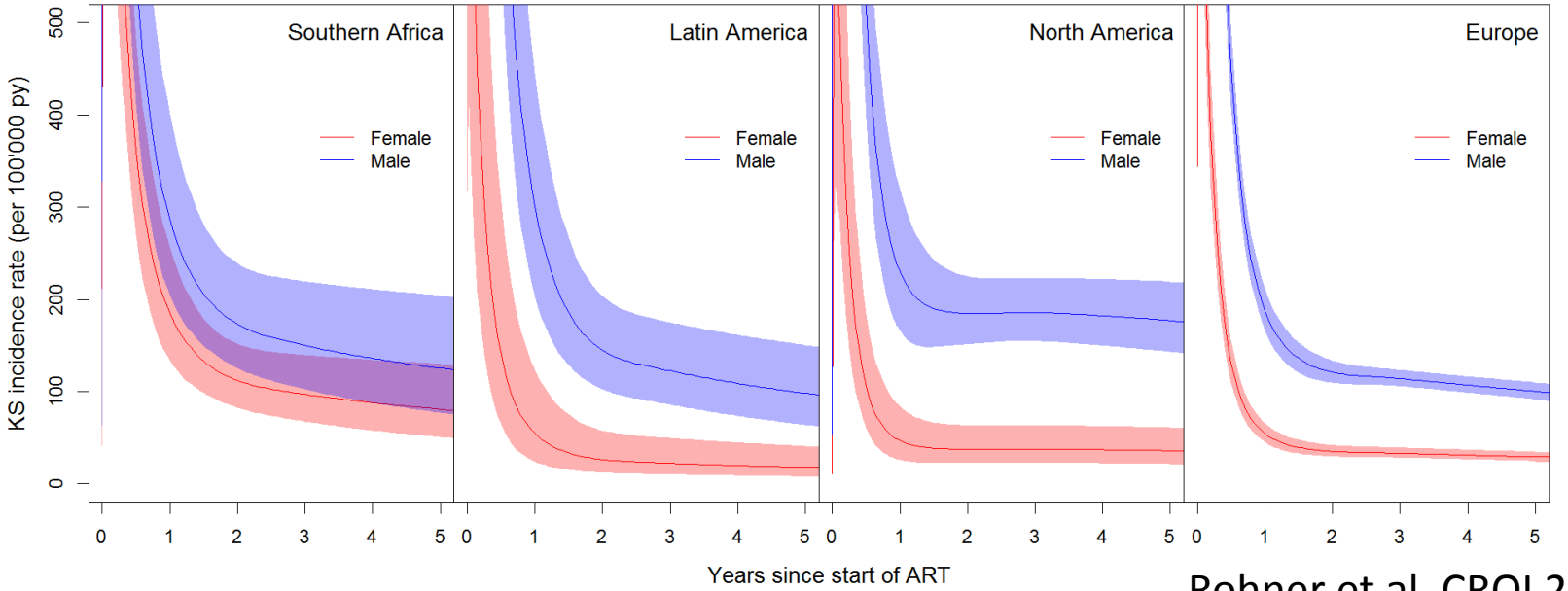


Total > 1 million

Kaposi sarcoma (KS) in adults

- 357,828 adults from Southern Africa, Latin America, North America and Europe included
- 1.4 million person-years
- 2,715 adults were diagnosed with KS after ART initiation
- Overall incidence rate: 196/100,000 pys (95% CI 189-204)

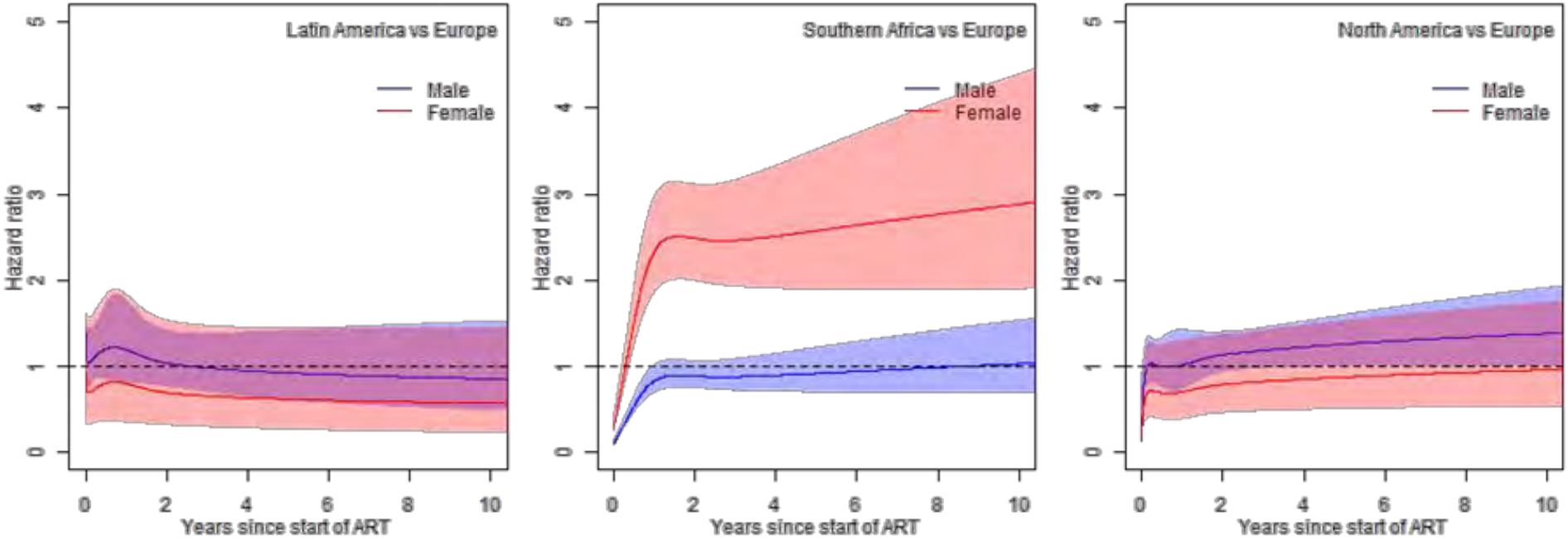
Figure: KS incidence rates by time since ART initiation in men and women, stratified by region.



Rohner et al, CROI 2016

KS in adults

Figure: Adjusted hazard ratio* and 95% CIs for the risk of developing KS in different regions compared to Europe.



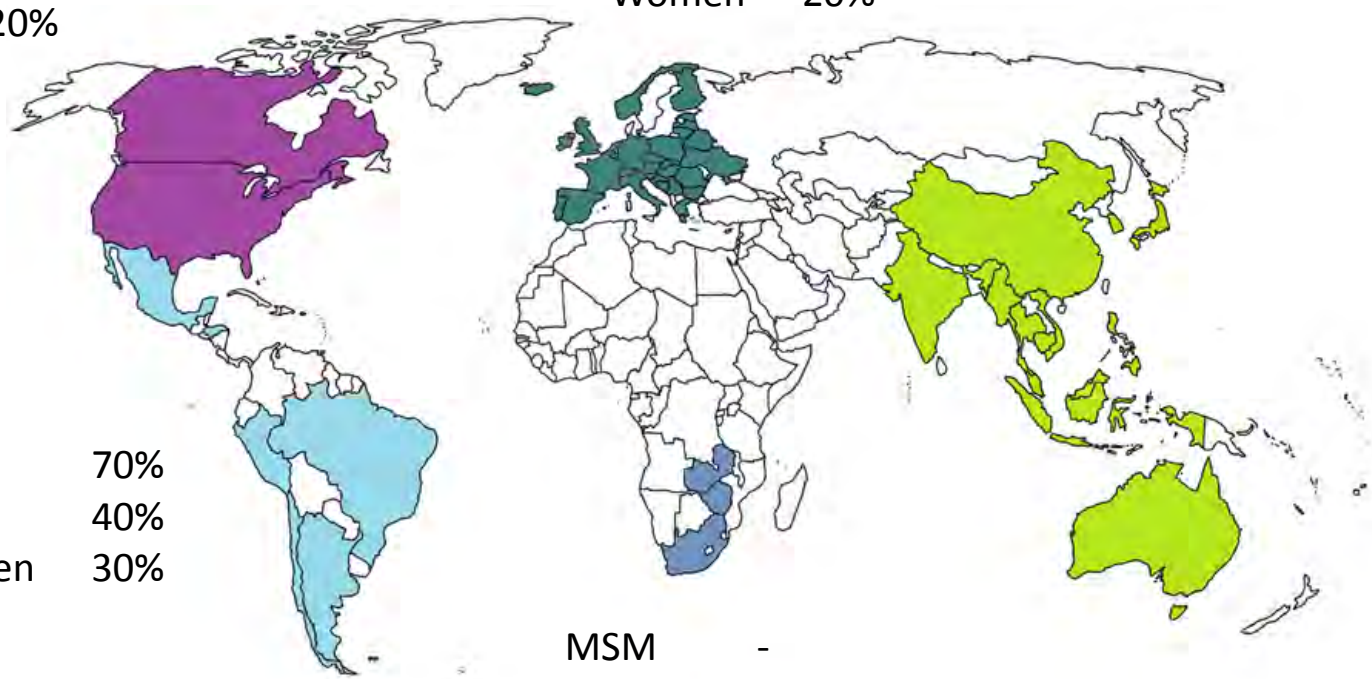
*Adjusted for age, sex and its interaction with region, time-updated CD4 counts and year of ART start

Rohner et al, CROI 2016

HHV-8 prevalence in HIV-positive adults

MSM 70%
Men 30%
Women 20%

MSM 60%
Men 30%
Women 20%



MSM 70%
Men 40%
Women 30%

MSM -
Men 50%
Women 50%

Adapted from Rohner et al, IJC 2016

KS in children

- 24,991 children from Asia, Eastern Africa, Southern Africa, and Europe included
- During 74,456 pys 26 children developed KS after ART initiation

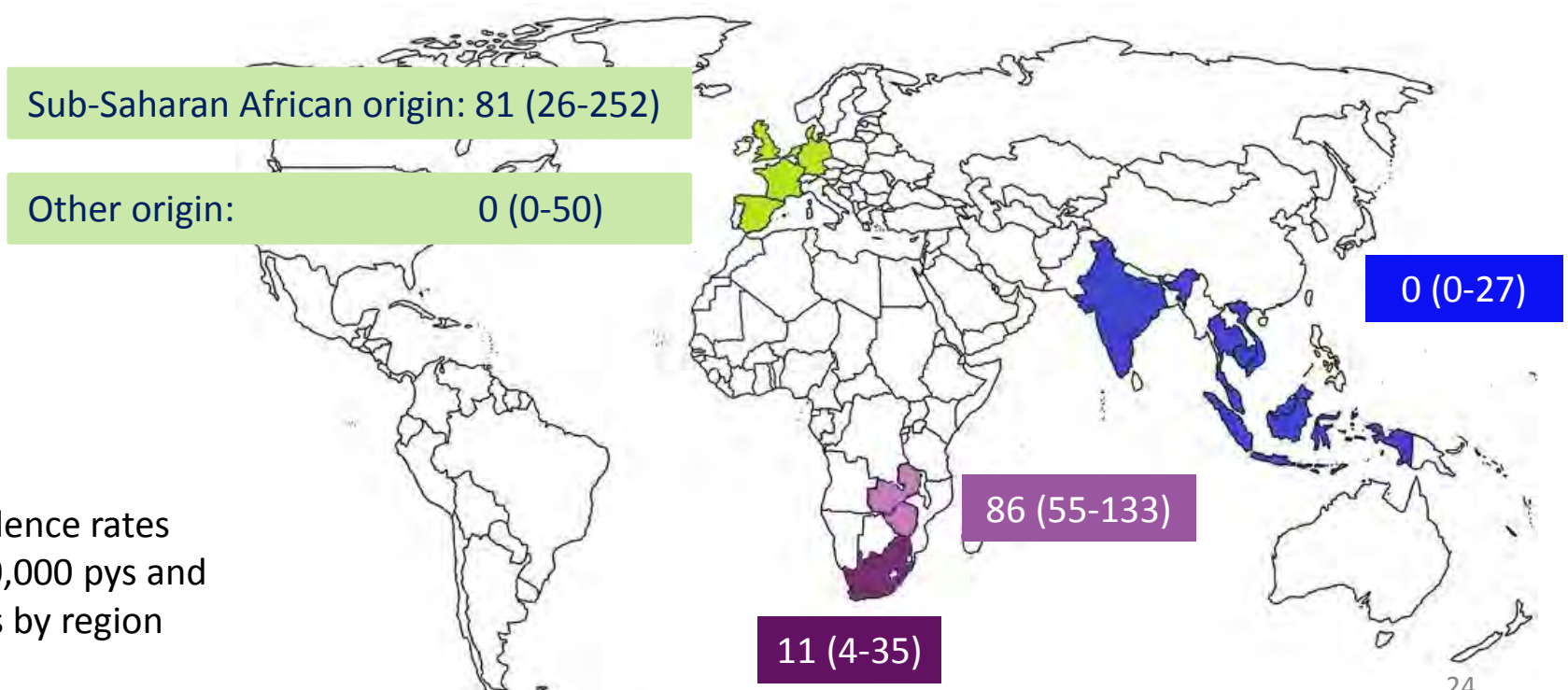
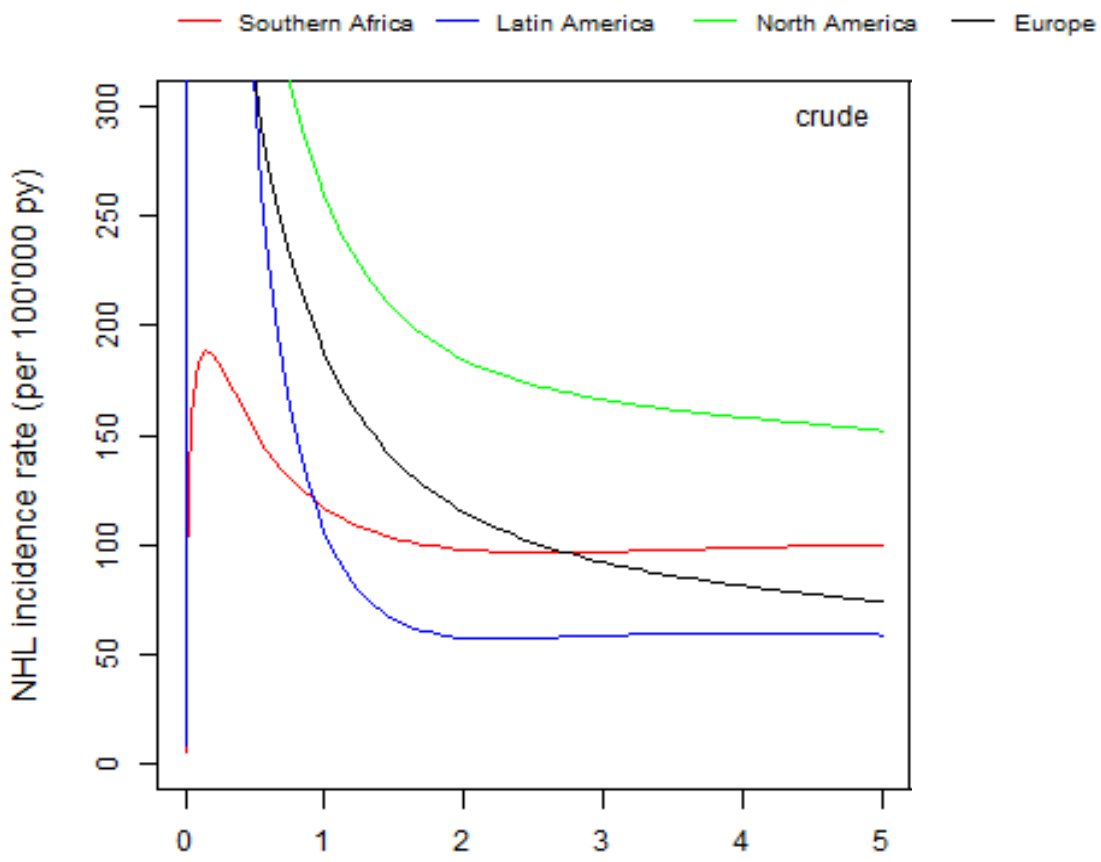


Figure:
KS incidence rates per 100,000 pys and 95% CIs by region

Rohner et al, under review CID

NHL in adults

- 210,178 adults from Europe, Southern Africa, Latin and North America
- 1.1 million pys after ART initiation, 1,598 adults developed NHL



Years since ART start

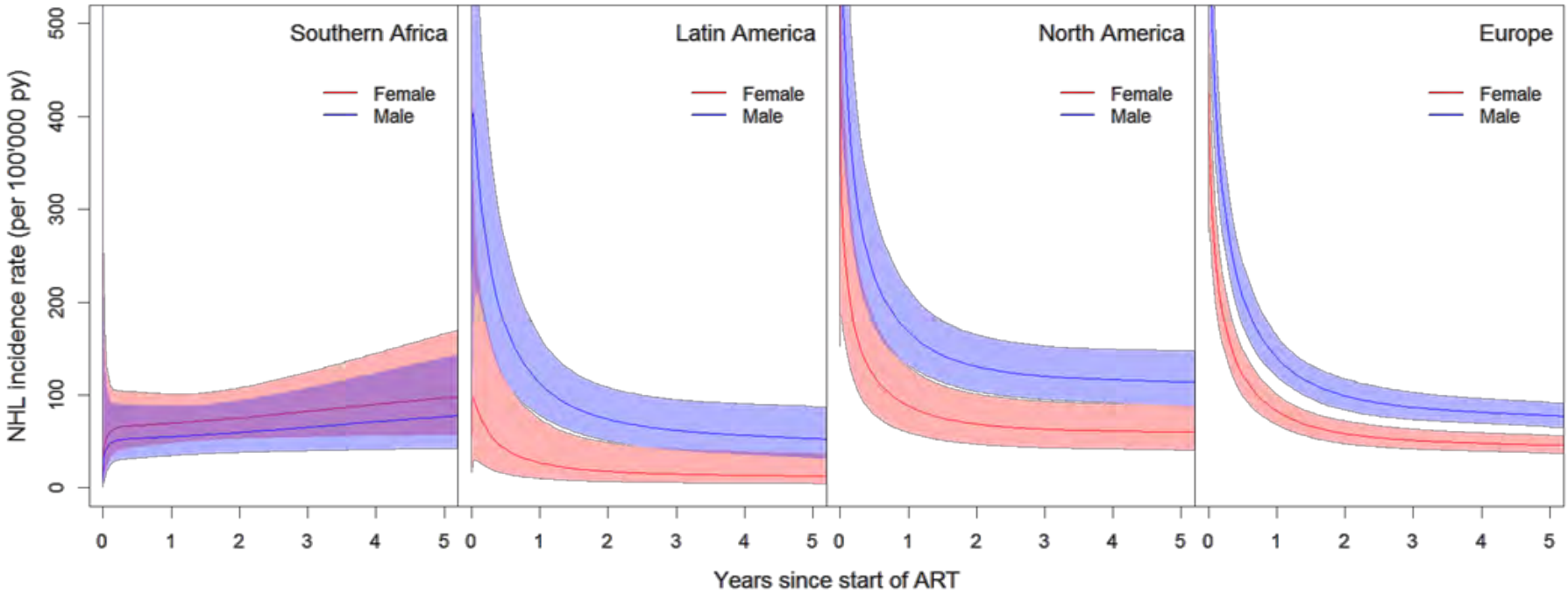
Rohner et al, ASCO 2016

NHL in adults

	Southern Africa	Latin America	North America	Europe
Adults (N)	22,136	8,677	17,001	162,229
Follow-up time* [years]	1.9 (0.7-3.9)	4.6 (1.9-8.1)	4.3 (1.7-8.5)	4.5 (1.8-8.5)
ART start year*	2008 (2006-2009)	2007 (2004-2010)	2001 (1998-2006)	2005 (2001-2009)
Age at ART start* [years]	36 (31-43)	36 (30-43)	40 (34-46)	37 (31-45)
Men (%)	37%	74%	75%	73%
MSM in men (%)	NR	57%	68%	55%
CD4 count at ART start* [cells/µl]	107 (43-176)	165 (61-273)	233 (92-378)	250 (126-368)

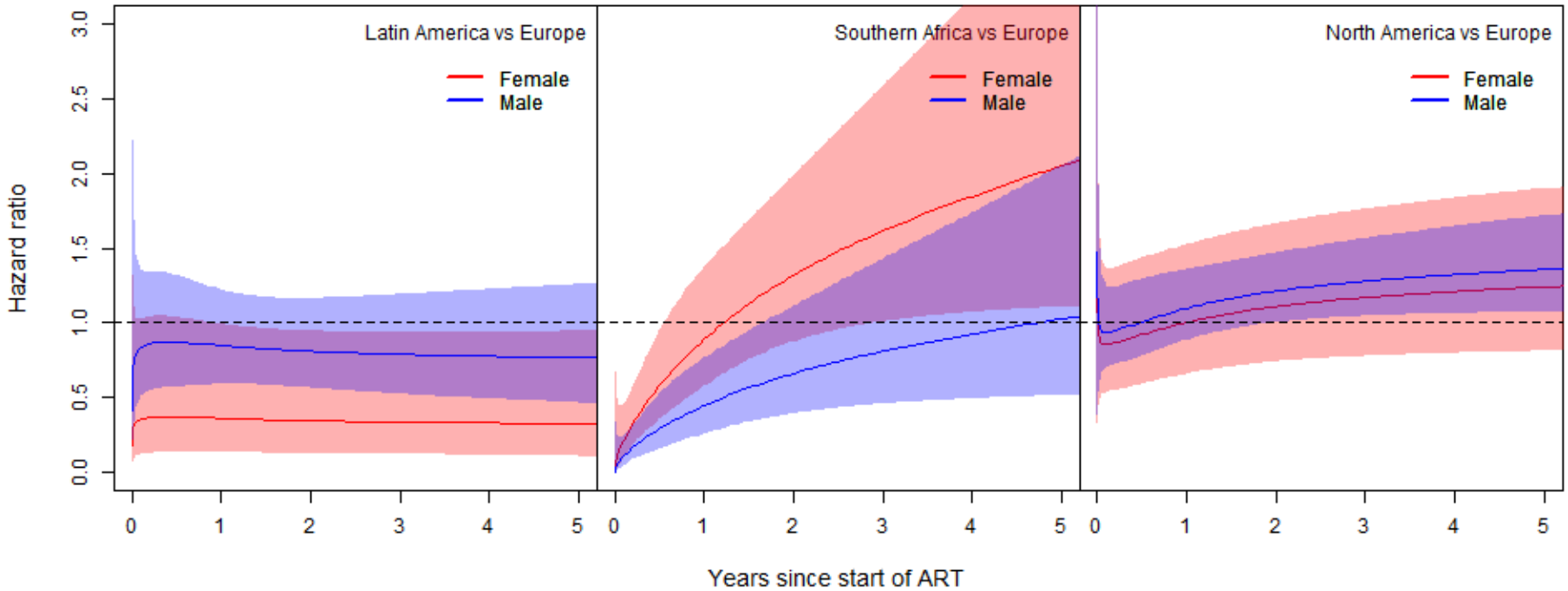
Rohner et al, ASCO 2016

NHL incidence rates



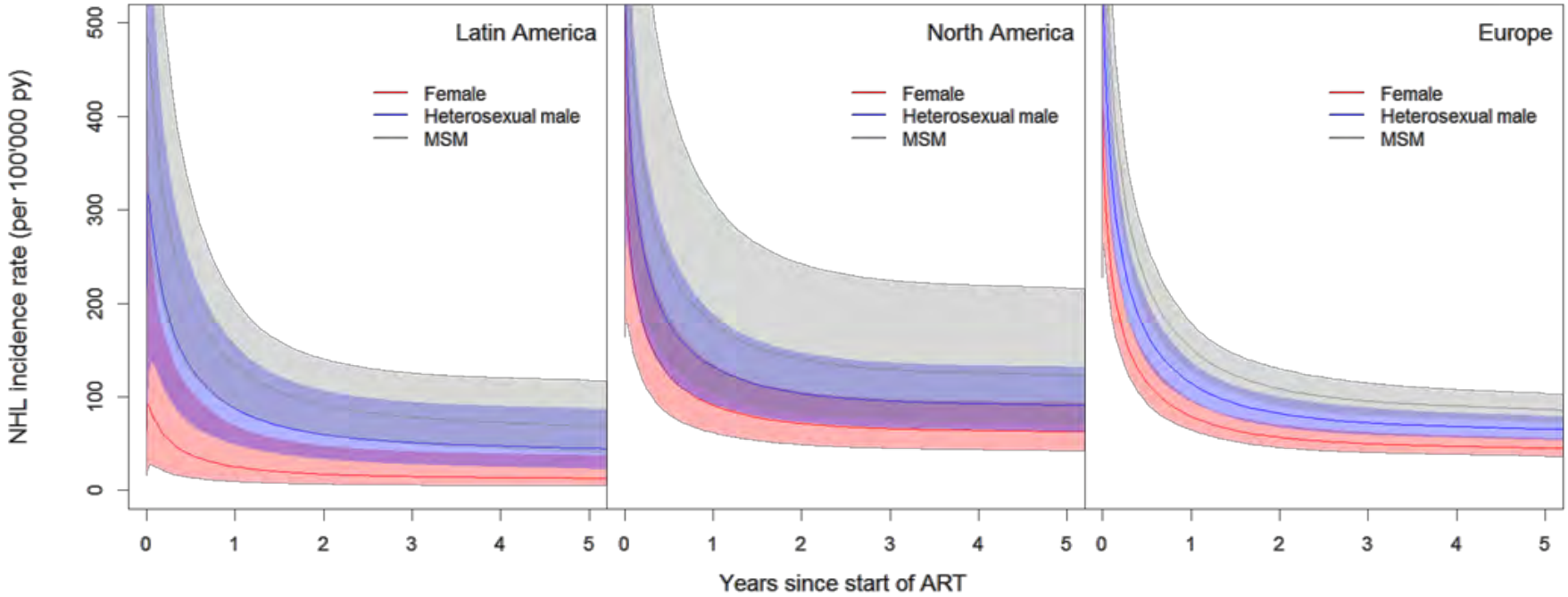
*Adjusted for age, sex and its interaction with region, time-updated CD4 counts, year of ART start and first-line regimen

NHL hazard ratios
Referent: Europe



*Adjusted for age, sex and its interaction with region, time-updated CD4 counts, year of ART start, first-line regimen, transmission mode

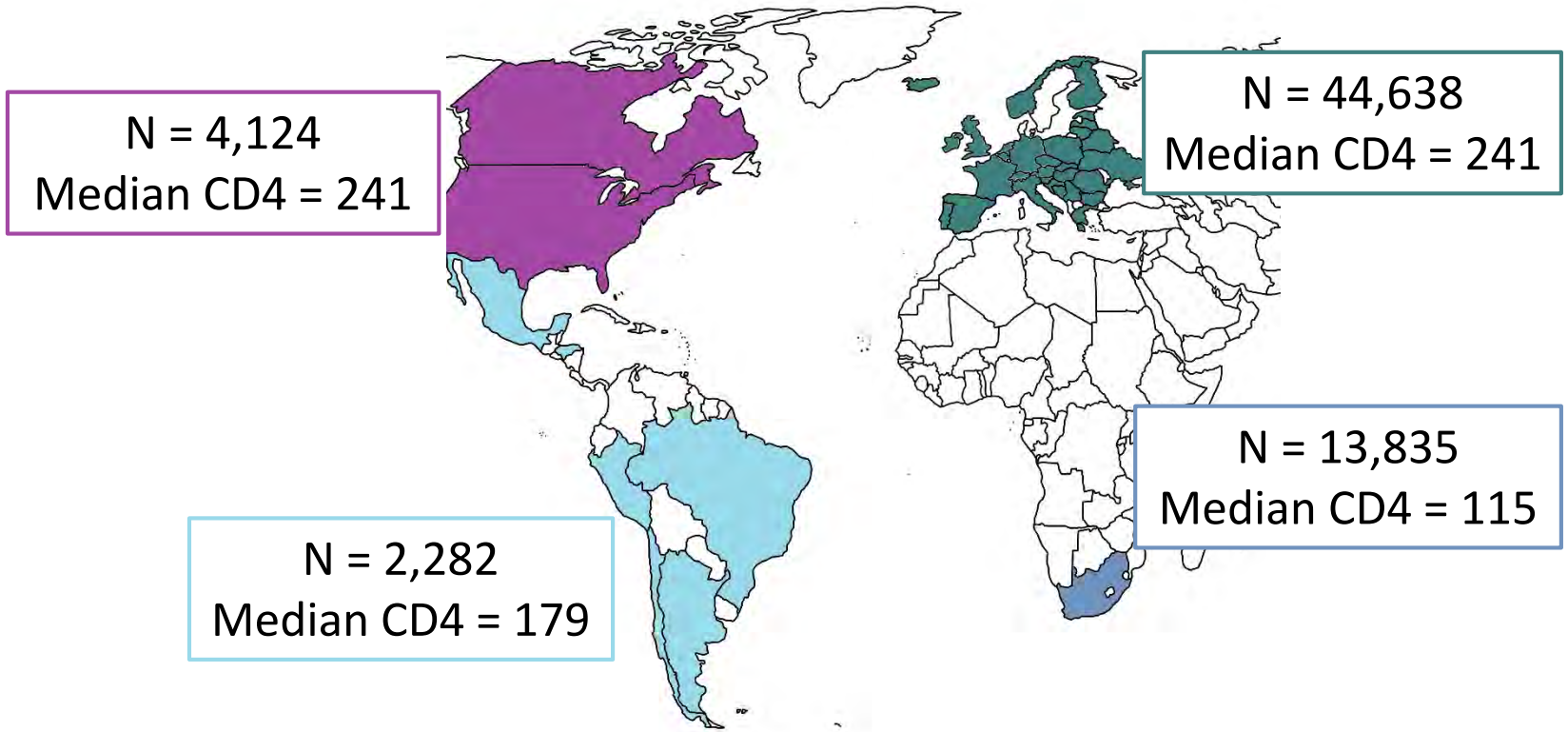
NHL incidence rates



*Adjusted for age, sex/mode and its interaction with region, time-updated CD4 counts, year of ART start and first-line regimen

Invasive cervical cancer (ICC)

- 64,879 women from Southern Africa, Latin America, North America and Europe included

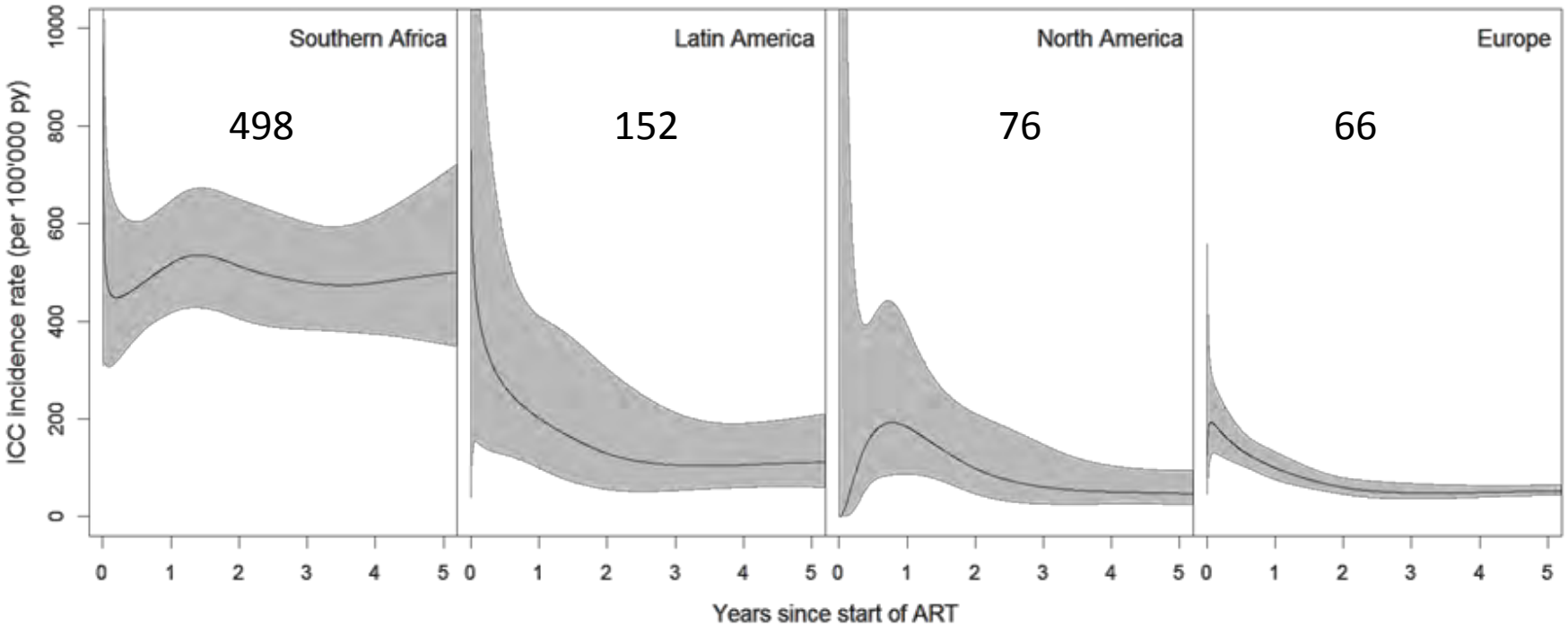


- During 320,686 person-years 376 women developed ICC

Rohner et al, CROI 2016

Invasive cervical cancer (ICC)

Figure: ICC incidence rate per 100,000 pys with 95% CIs by time since ART start, stratified by region.



Adjusted hazard ratios* compared to Europe at 5 years after ART start:

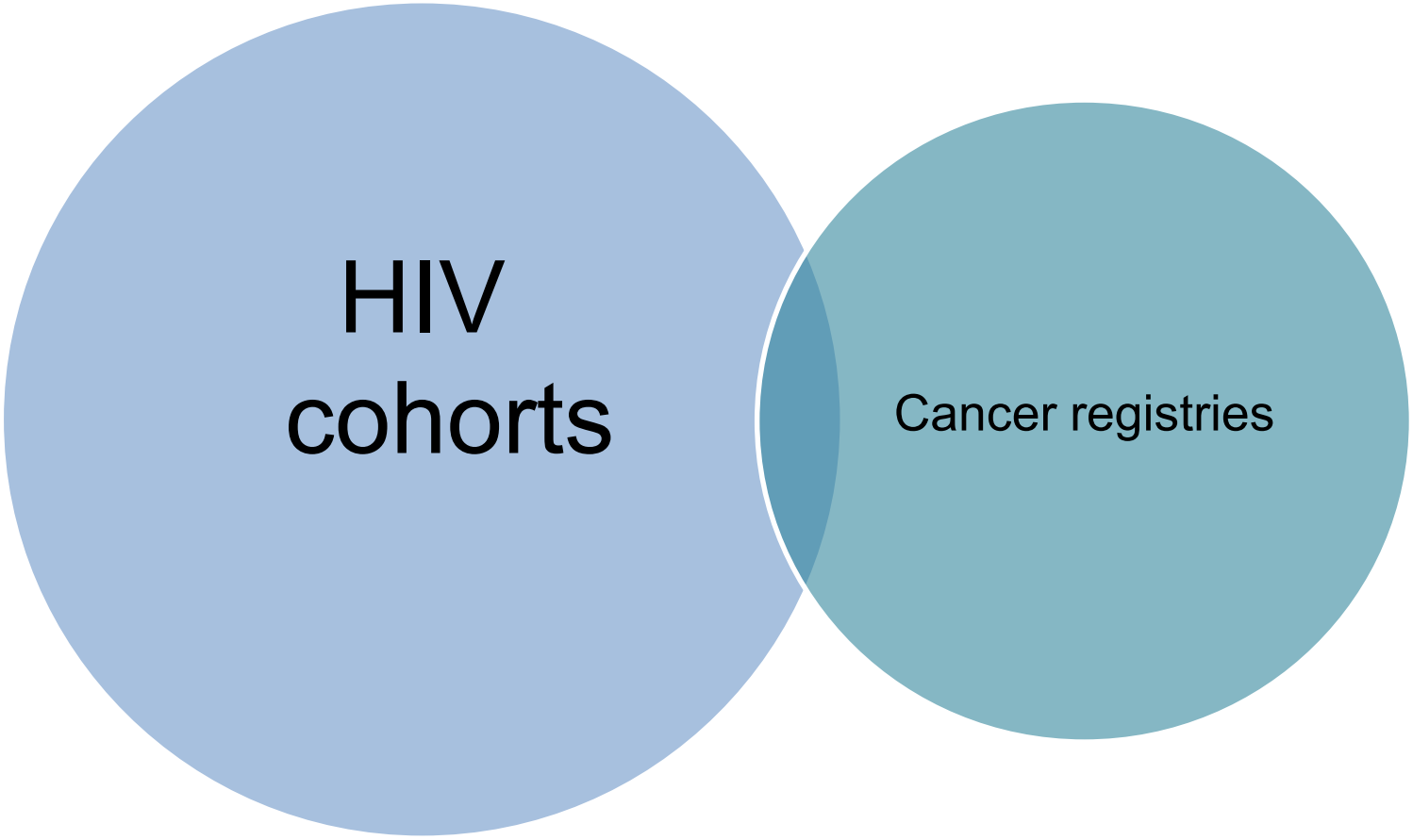
- North America: 0.7 (95% CI 0.3-1.4)
- Latin America: 2.2 (95% CI 1.2-4.2)
- Southern Africa: 12.4 (95% CI 7.8-20)

*Adjusted for age, year of ART start and current CD4 cell counts

Rohner et al, CROI 2016

PROBABILISTIC RECORD LINKAGES

Record linkage



Deterministic record linkage: folder numbers

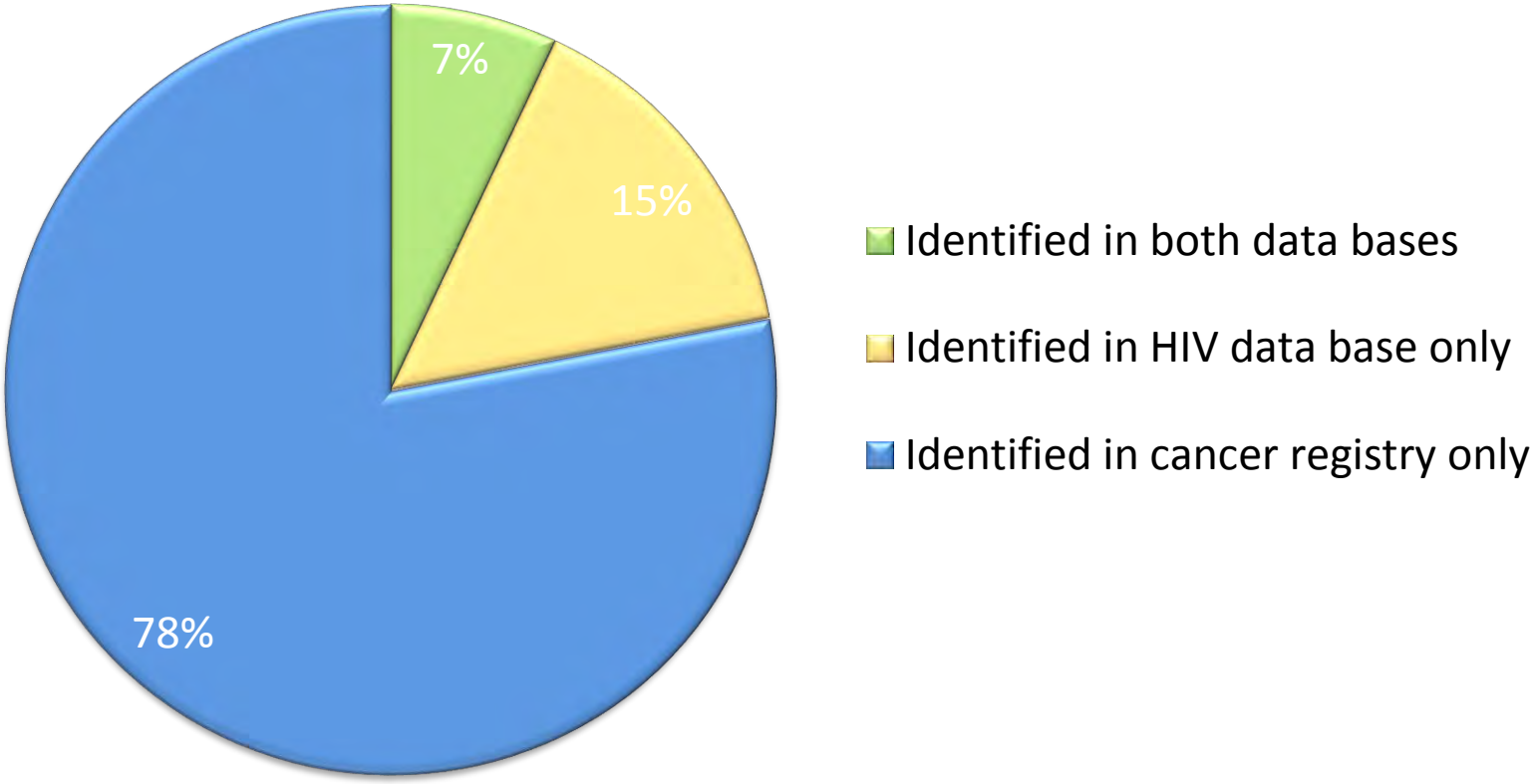
Probabilistic record linkage: names, date of birth, gender, other data

Cancer in children South Africa

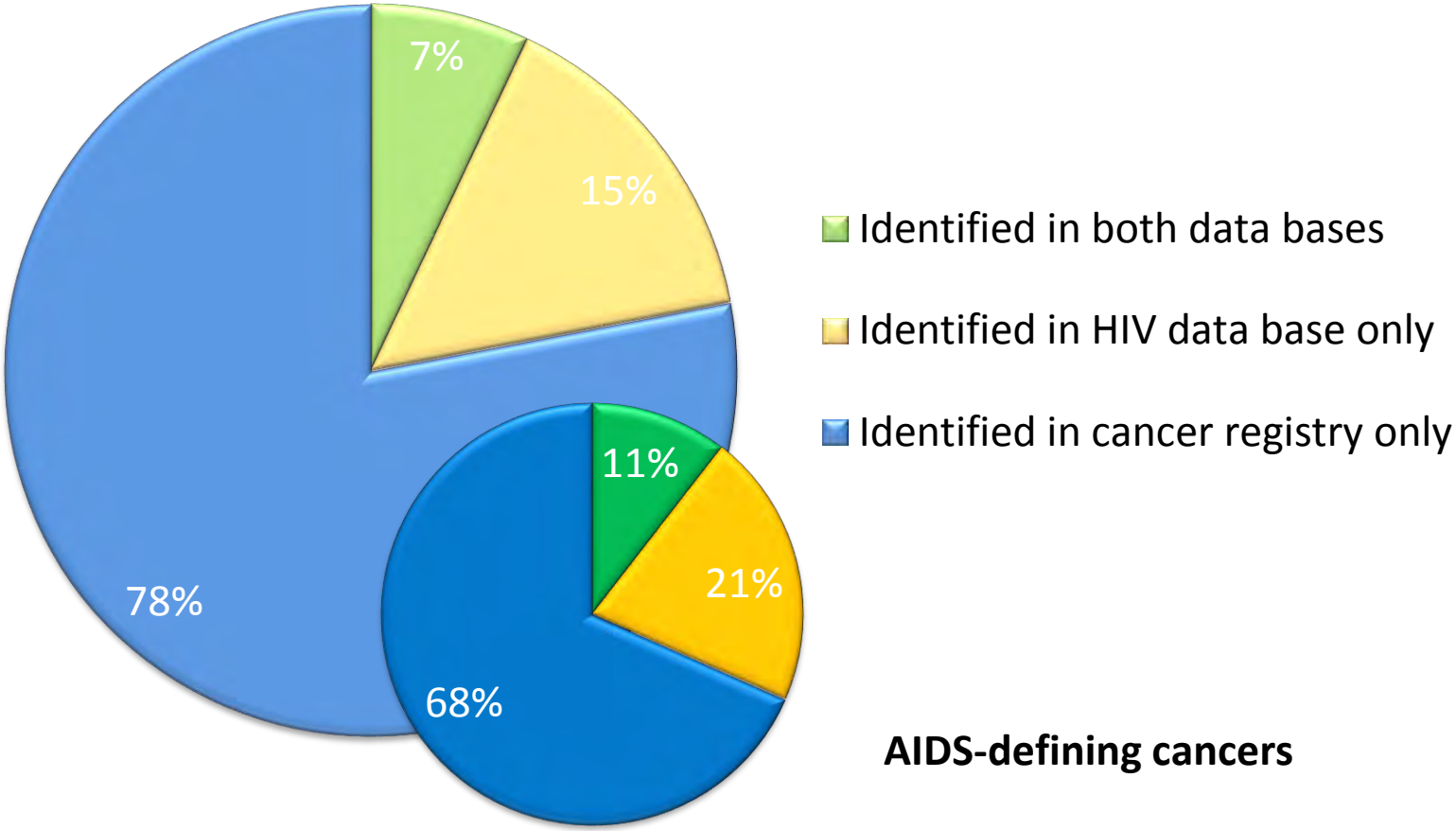
- > 10,000 HIV+ children enrolled in IeDEA-SA cohorts
- > 200 HIV+ cancer cases of pediatric oncology centers
- > 70 prevalent and incident cancer cases identified
- Overall cancer incidence rate:
  - 79/100,00 person-years (95% CI 53 – 116)

Bohlius et al, PIDJ 2016

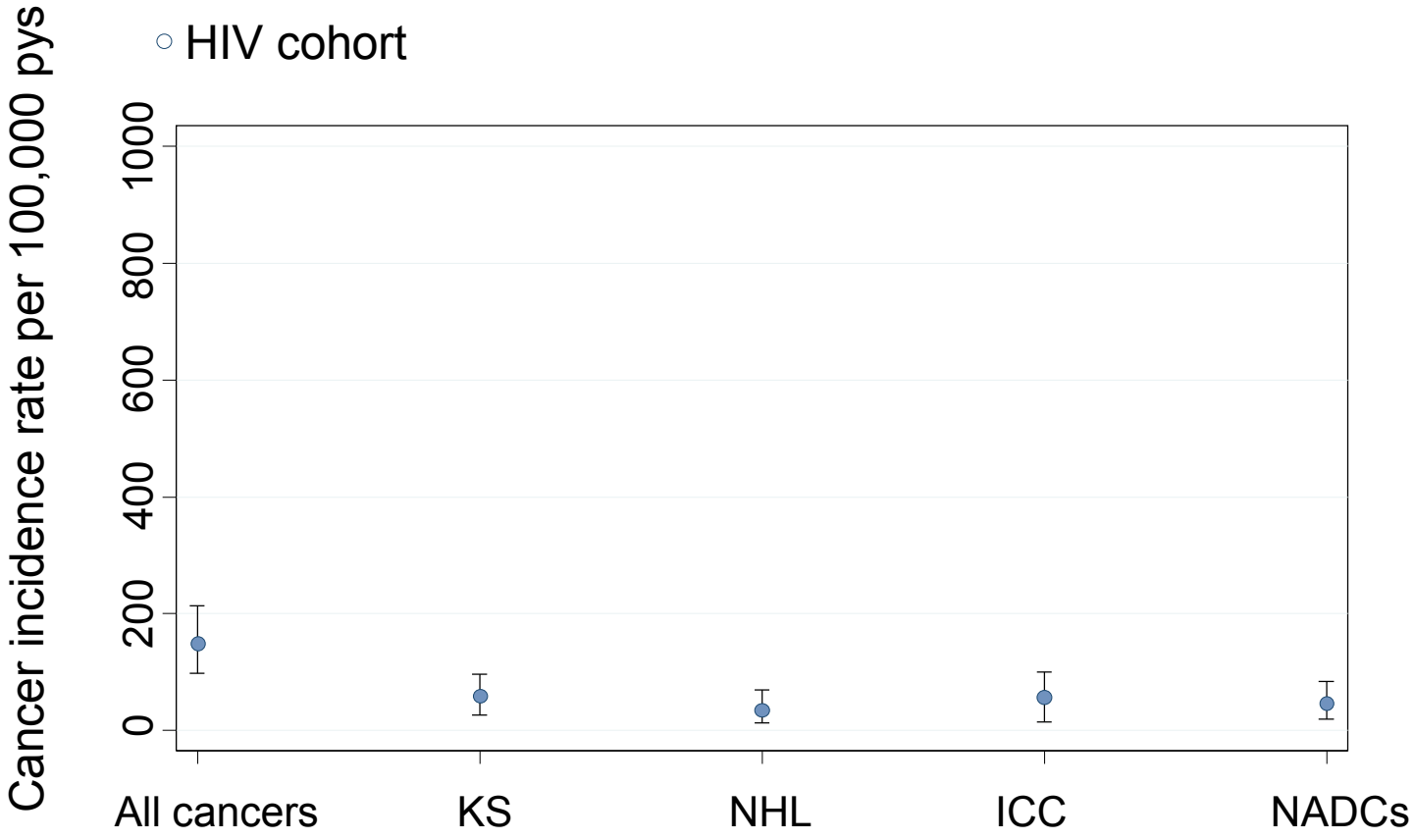
Cancer cases in children: data sources



Cancer cases in children: data sources

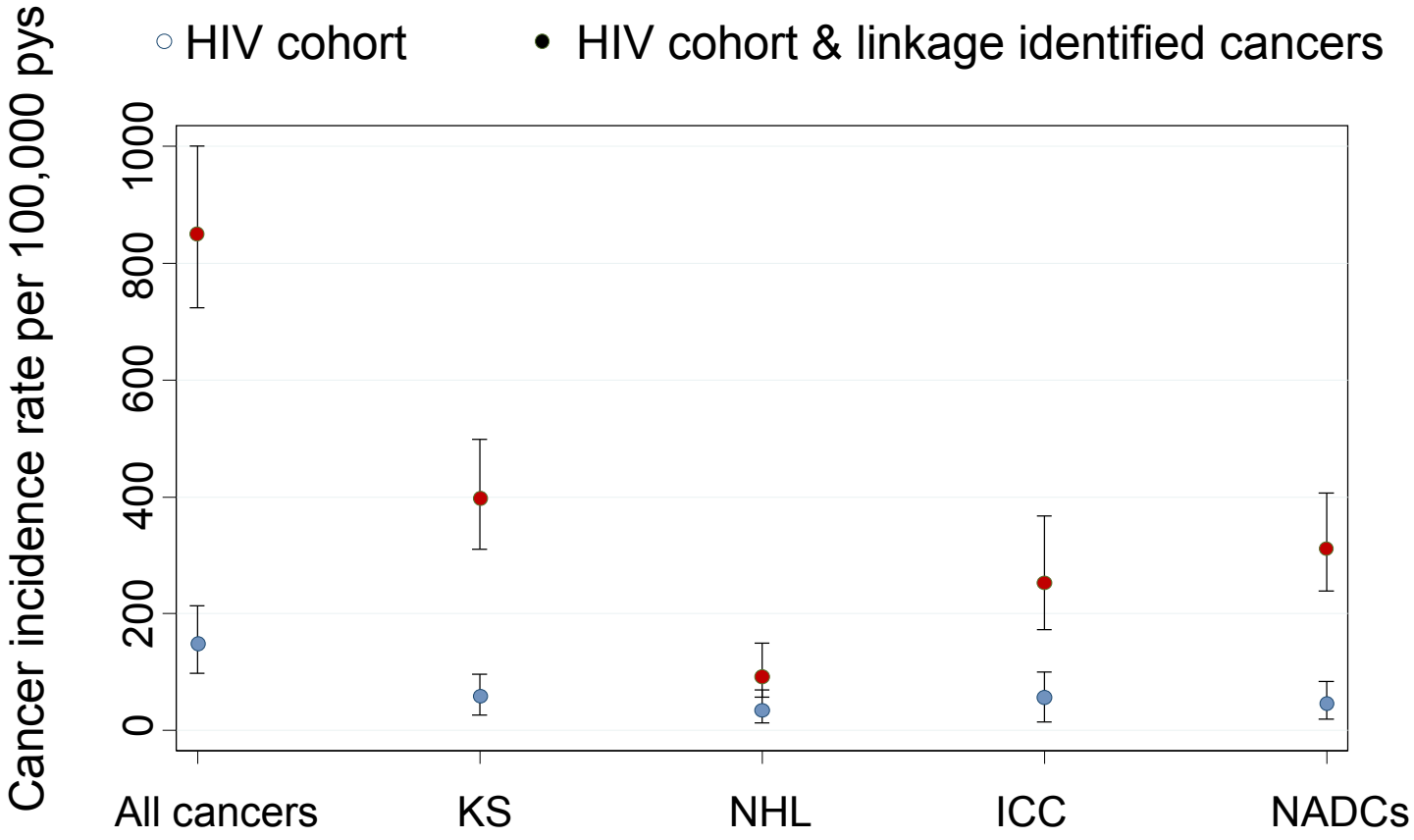


Impact on incidence rates adults in South Africa



Sengayi et al, ICJ 2016

Impact on incidence rates adults in South Africa



Sengayi et al, ICJ 2016

Limitations

- Only persons who initiated ART included
- Mode and completeness of cancer ascertainment vary between regions
- Data relevant for cancer risk analyses not necessarily available across all regions

Percentage of patients with available data based on the harmonized data set stratified by region

HIV data

	Asia-Pacific	CCASAnet	COHERE	IeDEA-SA	NA-ACCORD
Total N	16,524	11,742	306,482	556,641	28,877
Age	100	100	100	99.8	100
Gender	99.9	100	100	99.9	100
ART status known	100	100	99.5	97.8	100
ART regimen	100	100	100	100	100
CD4 cell count*	77.2	68.9	77.8	71.3	74.1
HIV RNA*	43.3	55.4	67.2	13.0	72.5
CDC/WHO stage*	93.7	61.2	94.4	81.7	100
Transmission risk group	98.2	87.5	92.6	22.7	91.9

* at ART initiation

Percentage of patients with available data based on the harmonized data set stratified by region

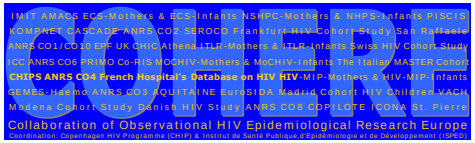
Data relevant for cancer analyses

	Asia-Pacific	CCASAnet	COHERE	IeDEA-SA	NA-ACCORD
Total N	16,524	11,742	306,482	556,641	28,877
Country of birth	13.9	NA	47.5	NA	NA
Race/ethnicity	88.0	NA	43.2	NA	97.2
Smoking, current	23.3	NA	9.1	NA	9.9
Smoking, packyears	NA	NA	NA	NA	5.4
Screened for cervical cancer	NA	NA	NA	NA	NA
HPV vaccination	NA	NA	NA	NA	NA
HBV vaccination	12.4	NA	NA	NA	NA
HHV-8 serostatus	NA	NA	NA	NA	NA

NA, not available

Conclusions

- Despite ART availability, the risk of developing cancer remains high in HIV-positive persons
- Regional variation in cancer risk might be explained by differences in
  - Completeness of cancer ascertainment
  - Prevalence of oncogenic viruses (HHV-8, HPV)
  - HIV epidemics
  - Access to health care
- To monitor the cancer epidemic in HIV-positive populations cohort studies identifiying AIDS defining and non AIDS defining cancers are needed
- Data for key risk factors, such as screening for cervical cancer and HPV vaccination, should be collected at patient level
- Probabilistic record linkages with cancer registries may help to reduce underrecording of cancer cases in the HIV cohorts



Acknowledgements

Project leaders and statistical analysis:

Juan Berenguer, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Mary-Anne Davies, Julia del Amo, Maria Dorrucci, David Dunn, Matthias Egger, Hansjakob Furrer, Marguerite Guiguet, Sophie Grabar, Ali Judd, Ole Kirk, Olivier Lambotte, Valériane Leroy, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose Mª Miró, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Andrew Phillips, Massimo Puoti, Michael Schomaker, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, , Marc van der Valk, Linda Wittkop, Natascha Wyss

Project working group:

Gary Clifford, Jonathan Sterne, Julia Bohlius, Eliane Rohner, Marcel Zwahlen, Margaret May, Maria Campbell, Matthias Egger, Natascha Wyss, Rana Chakraborty, Sylvia Franceschi, Kurt Schmidlin, Annelies Verbon, Diana Gibb, Antoni Noguera-Julian, Claudia Fortuny, Toni Soriano, Niels Obel, Sophie Grabar, Norbert Brockmeyer, Geneviève Chêne

Regional Coordinating Centres: Bordeaux RCC: Diana Barger, Christine Schwimmer, Monique Termote, Linda Wittkop; Copenhagen RCC: Maria Campbell, Casper M. Frederiksen, Nina Friis-Møller, Jesper Kjaer, Dorthe Raben, Rikke Salbøl Brandt

Sources of funding: The COHERE study group has received unrestricted funding from: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, the Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. A list of the funders of the participating cohorts can be found on the Regional Coordinating Centre websites at http://www.cphiv.dk/COHERE/tabid/295/Default.aspx and http://etudes.isped.u-bordeaux2.fr/cohere."

Steering committee:

Executive Committee: Stéphane de Wit (Chair, St. Pierre University Hospital), Jose Mª Miró (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Antonella Castagna (San Raffaele), Julia del Amo (CoRIS), Amanda Mocroft (EuroSida), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre)

Steering Committee - Contributing Cohorts: Ali Judd (AALPHI) Robert Zangerle (AHIVCOS),Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Linda Wittkop (ANRS CO13 HEPAVIH), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo Conejo (CORISPES-Madrid), Antoni Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Roger Kouyos (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Deborah Konopnick (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Anders Sönnerborg (Swedish InfCare), Carlo Torti (The Italian Master Cohort), Caroline Sabin (UK CHIC), Ramon Teira (VACH), Myriam Garrido (VACH). David Haerry (European AIDS Treatment Group)

Paediatric cohort representatives: Ali Judd, Pablo Rojo Conejo

European AIDS Treatment Group: David Haerry

Acknowledgements

Sponsoring Institutions

National Institutes of Health (NIH)

National Institute of Allergy and Infectious Diseases **(NIAID)**: Carolyn F.M. Williams, Rosemary McKaig, Melanie Bacon, Lori Zimand, Robin Huebner, Gerald Sharp

National Institute for Child Health Development **(NICHD)**: Rohan Hazra

National Cancer Institute **(NCI)**: Geraldina Dominguez, Kishor Bhatia

Coordinating Center: IeDEA Network Coordinating Center (INCC) at Vanderbilt: Mary Lou Lindegren & C. William Wester, Dana Walker, Kristin Centers, Toni Hill

Regions and site PIs

NA ACCORD: (Region 1)
Richard Moore (Johns Hopkins University)
Michael Saag (University of Alabama)

CCASAnet: (Region 2)
Cathy McGowan (Vanderbilt University)
Pedro Cahn (Fundación Huésped, Argentina)

Asia-Pacific: (Region 5)
David Cooper, Matthew Law (University of New South Wales), Annette Sohn (amfAR TREAT Asia)

Southern Africa: (Region 11)
Matthias Egger (University of Bern)
Mary-Ann Davies (University of Cape Town)

Project working group:

Michael Vinikoor, Kathryn Stinson, Cleophas Chimbetete, Hans Prozesky, Brian Eley, Karl Technau, Helena Rabie, Shobna Sawry, Daniela Garone, Roalind Wainwright, Alan Davidson, D Crisitna Stefan, Mhairi Maskew, Mary-Ann Davies, Janet Giddy, Annette Sohn, Arthur Chen, Awachana Jiamsakul, Nicolas Durier, Chuenkamol Sethaputra, Kathy Petoumenos, Valeria Fink, Cathrine McGowan, Pedro Cahn, Beatriz Grinsztein, Gina Perez, Karu Jayathilake, Gypsyamber D'Souza, Richard Moore, Michael Silverberg, M John Gill, Sonia Napravnik, Chad Achenbach, James Goedert, Mari Kitahata, Pragna Patel, Rob Dubrow.

Working Groups – Chairs

Executive Committee
Matthias Egger (University of Bern; Bern, Switzerland)

Cancer
Julia Bohlius (University of Bern; Bern, Switzerland), Jeff Martin (University of California, San Francisco; CA, USA)

Pediatrics
Rachel Vreeman (AMPATH / Kenya; Indiana University School of Medicine; Bloomington, IN, USA)

Tuberculosis
Marie Ballif (University of Bern; Bern, Switzerland), April Pettit (Vanderbuilt University; Nashville, TN, USA)

Clinical Outcomes / Pharmacovigilance
Kathy Anastos (Albert Einstein/Montefiore; USA)

Site Assessment
Denis Nash (Hunter College; New York, NY, USA); C. William Wester (Vanderbilt University; Nashville, TN, USA)

Data Harmonization
Beverly Musick (Indiana University; Bloomington, IN, USA)

Funding: Supported by the National Institute Of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), of the U.S. National Institutes of Health (NIH) under Award Number Southern Africa: U01AI069924, Asia-Pacific: U01AI069907, Central Africa: U01A096299, East Africa: U01AI069911, Caribbean, Central, and South America: U01AI069923, West Africa: U01AI069919, NA-ACCORD: U01-AI069918 and the IeDEA Network Coordinating Center at Vanderbilt: U01A1096186.

BACKUP

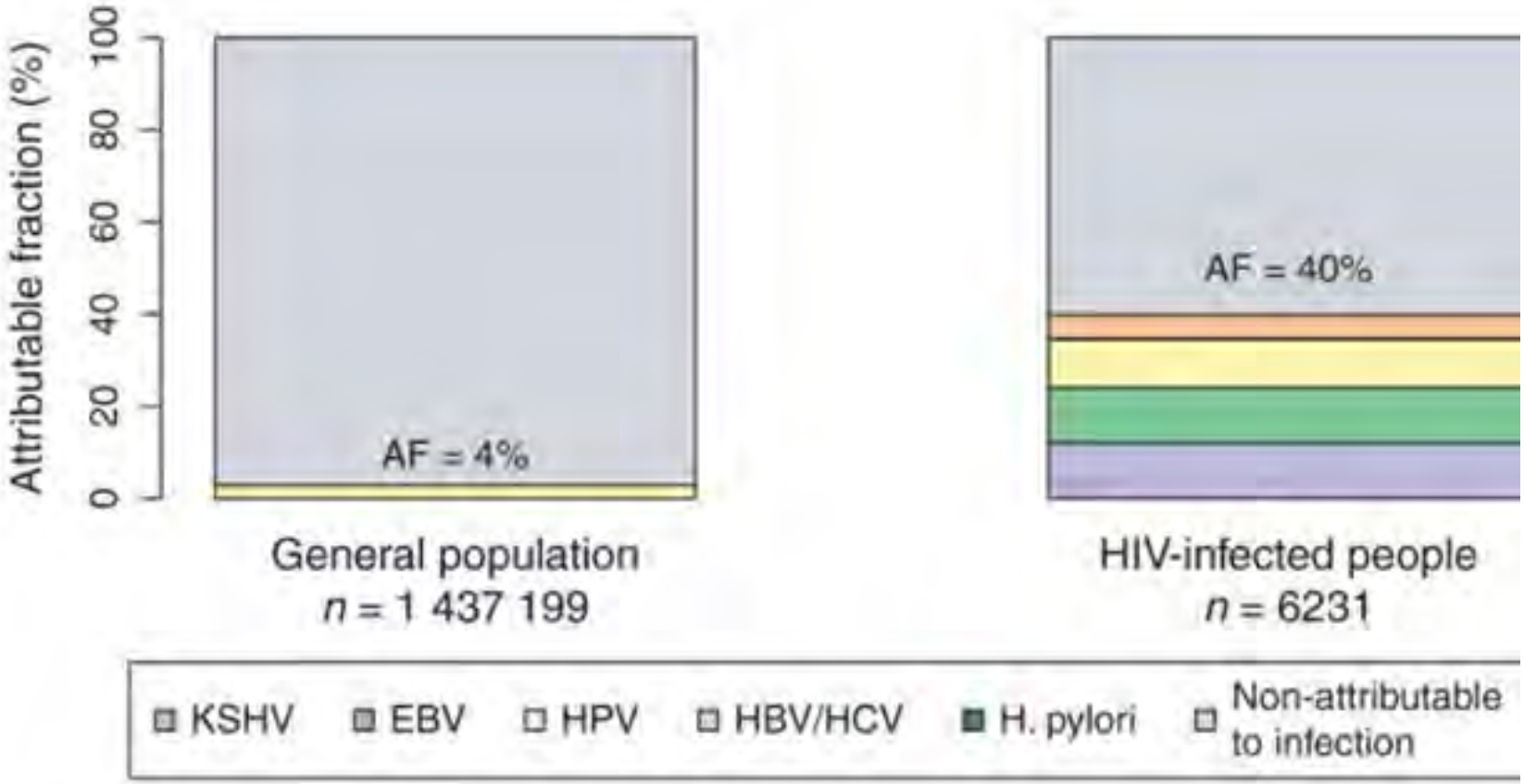
Cancer incidence rates adults on ART in South Africa

Type of cancer	Men		Women		Total	
	n (%)	Incidence rate[1]	*n* (%)	Incidence rate[1]	*n* (%)	Incidence rate[1]
Total	48 (100)	752 (567–1,017)	94 (100)	949 (776–1,172)	142 (100)	877 (744–1,041)
ADCs	31 (64.6)	487 (345–712)	64 (68.1)	653 (512–845)	95 (66.9)	592 (485–731)
KS	29 (60.4)	457 (320–677)	39 (41.5)	417 (306–583)	68 (47.9)	432 (341–555)
ICC	–	–	27 (28.7)	259 (179–390)	27 (19.0)	259 (179–390)
NHL	6 (12.5)	88 (40–235)	9 (9.6)	83 (44–178)	15 (10.6)	85 (52–150)
NADCs	18 (37.5)	271 (172–454)	32 (34.0)	307 (219–445)	50 (35.2)	294 (223–395)
Breast	–	–	11 (11.7)	94 (53–185)	11 (7.7)	94 (53–185)
Ano-genital other than cervix	1 (2.1)	–	10 (10.6)	105 (57–214)	11 (7.7)	72 (42–146)
Conjunctiva	2 (4.2)	37 (8–411)	6 (6.4)	55 (25–146)	8 (5.6)	49 (25–110)
Lip, oral cavity and pharynx	5 (10.4)	80 (34–239)	2(2.1)	18 (4–185)	7 (4.9)	41 (20–99)
Other	14 (29.2)	193 (115–348)	13 (13.8)	118 (70–217)	27 (19.0)	146 (101–219)

Analysis based on 6,370 patients on ART
Follow-up time: 15,976 person-years

Sengayi et al, ICJ 2016

Cancers attributable to infections USA



De Martel et al 2015