Management of HIV in the peri-transplant period

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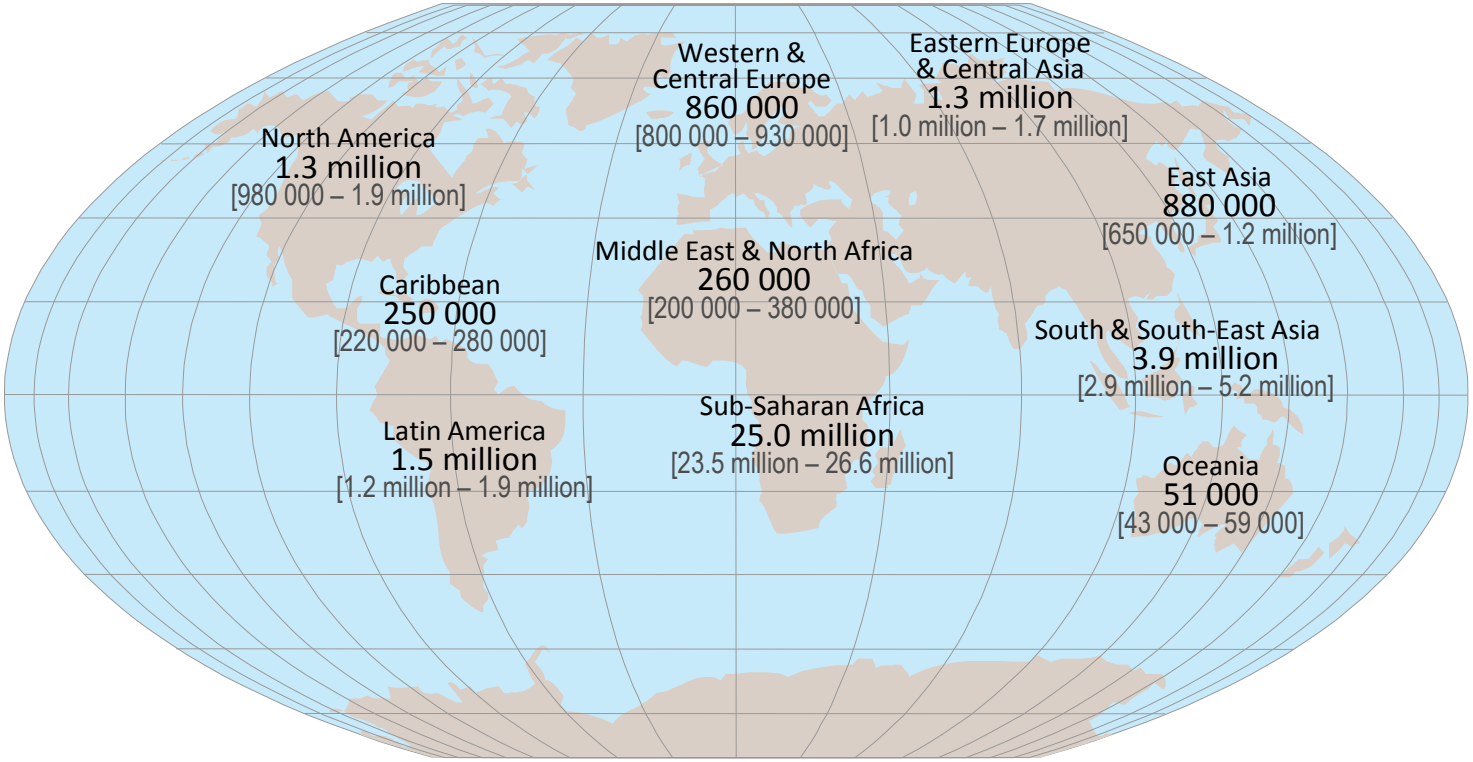
WBMT Symposium, Cape Town, 16 November 2014

Overview

- HIV in South Africa
- Key principles of antiretroviral therapy (ART)
- HCT in HIV+ patients
- Drug interactions
- Toxicities
- Prophylaxis
- HIV cure?

Adults & children estimated to be living with HIV | 2012



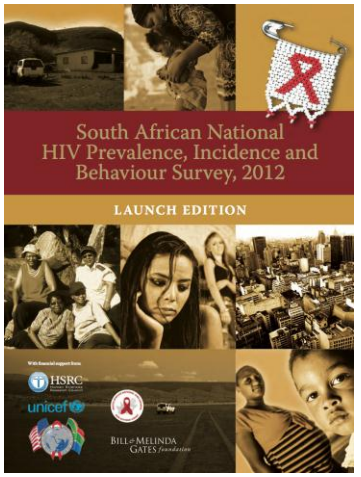
Global total: 35.3 million [32.2 million – 38.8 million]

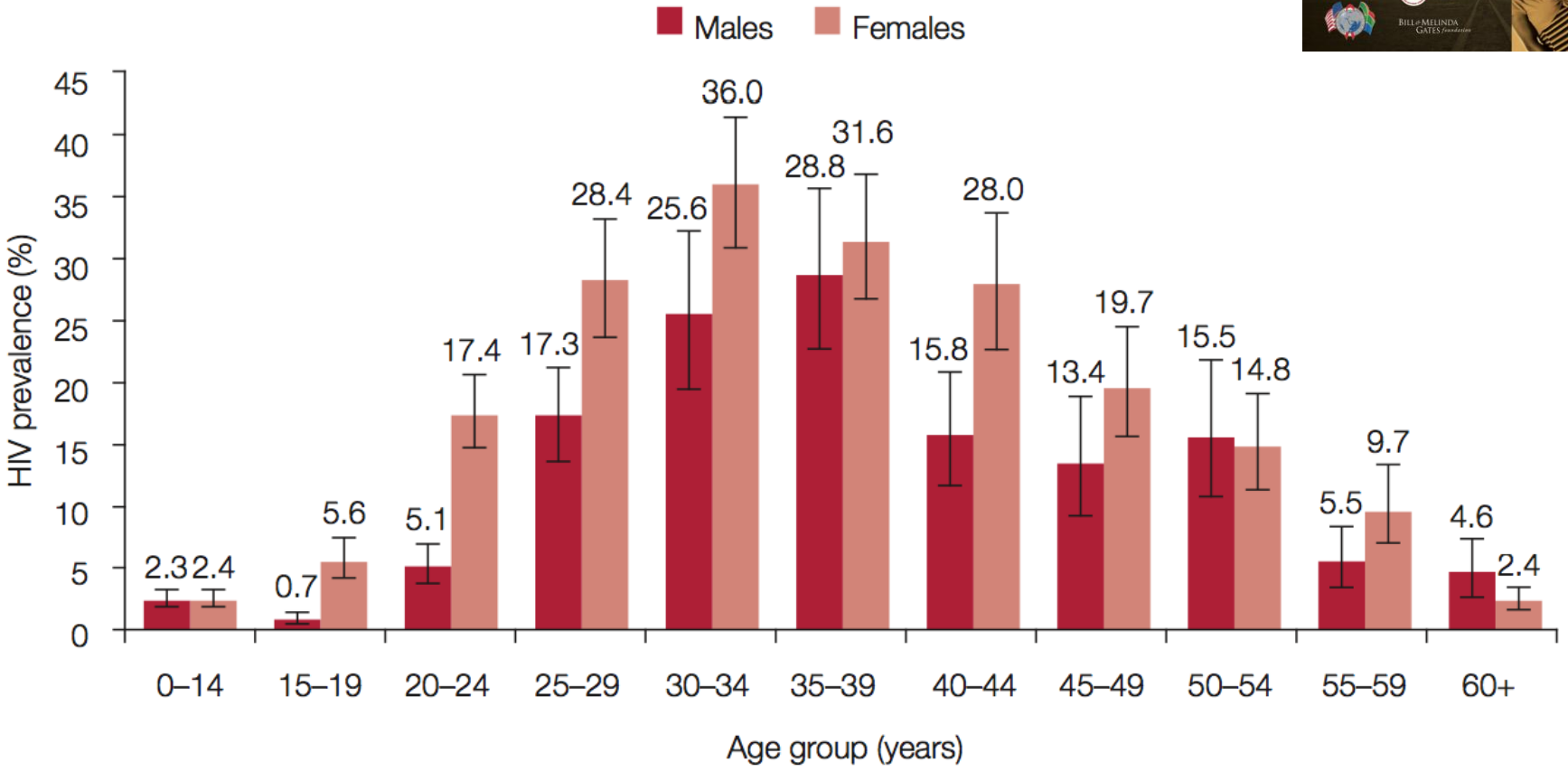
25 million (71%) in sub-Saharan Africa

UNAIDS Global Report 2013

HIV prevalence in South Africa

6.4 million people HIV-infected (12%)





HSRC survey, 2012

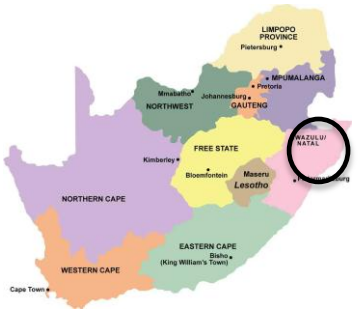
Antiretroviral therapy (ART) in SA

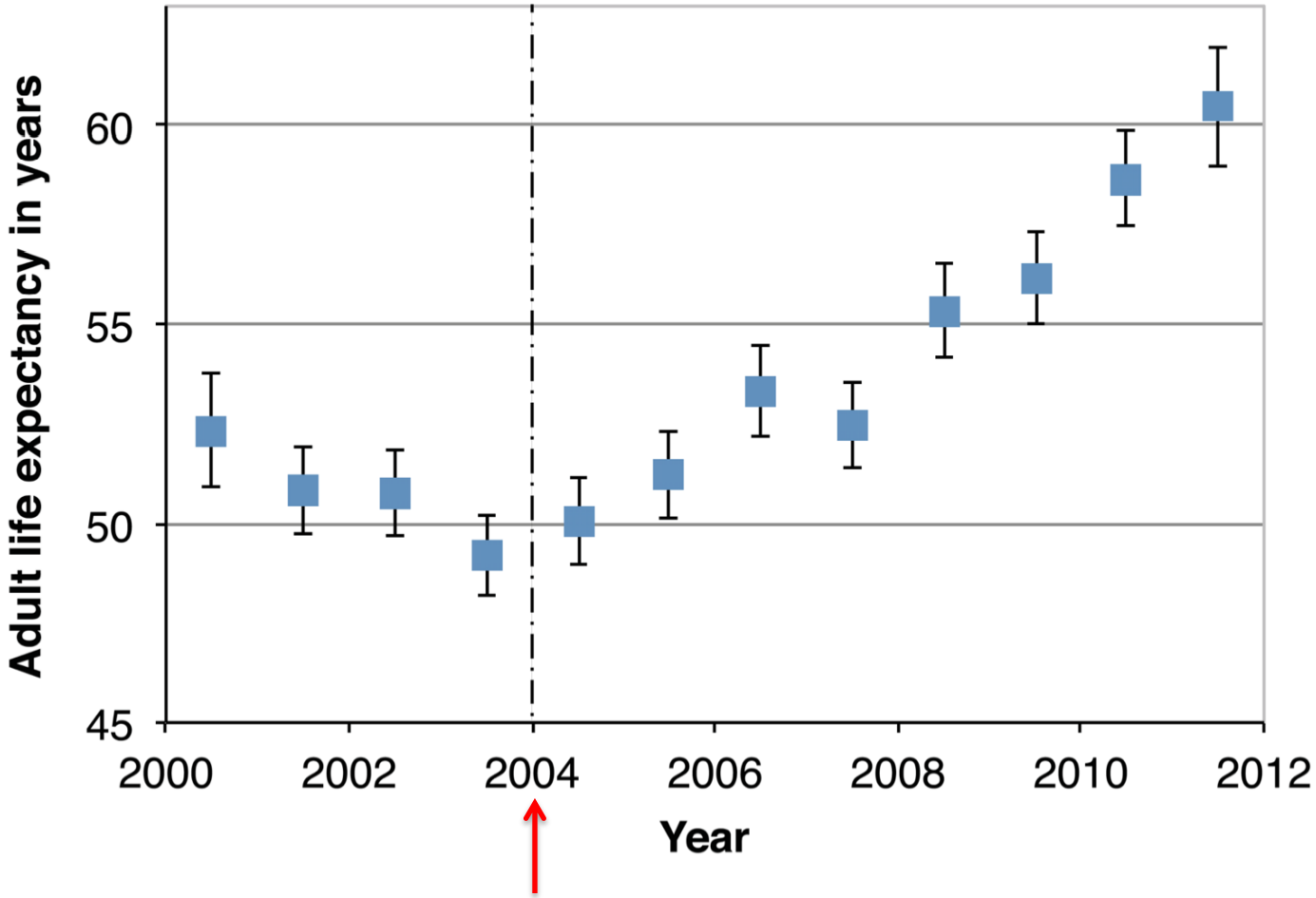
- Available in public sector since 2004
- Over 2 million people on ART
- Indications for starting (1 January 2015)
  - CD4 ≤ 500
  - Stage 3 or 4, TB, hepatitis B
  - Pregnancy
  - Serodiscordant couple

Benefits of ART

- Suppression of HIV viral replication
  - Viral load decreased 90-99% within 2 weeks
  - Majority suppressed < 50 copies/ml by 6 months
- CD4 count recovery
  - Average ~75 cells/ul in 1st month then ~75 cells/ul per year
- Prevention of HIV-related opportunistic infections, malignancies and organ-specific pathologies

Life expectancy in rural Kwazulu-Natal





National ART programme commenced in 2004

Bor, Science 2013;339:961

OPEN ACCESS Freely available online

PLOS | MEDICINE

Life Expectancies of South African Adults Starting Antiretroviral Treatment: Collaborative Analysis of Cohort Studies

Leigh F. Johnson[1]*, Joel Mossong[2], Rob E. Dorrington[3], Michael Schomaker[1], Christopher J. Hoffmann[4,5], Olivia Keiser[6], Matthew P. Fox[7,8], Robin Wood[9], Hans Prozesky[10,11], Janet Giddy[12], Daniela Belen Garone[13], Morna Cornell[1], Matthias Egger[6], Andrew Boulle[1], for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration[¶]

Average life expectancy of men starting ART varied between 27.6 y at age 20 y and 10.1 y at age 60 y.

Estimates for women at the same ages were substantially higher, at 36.8 y and 14.4 y, respectively.

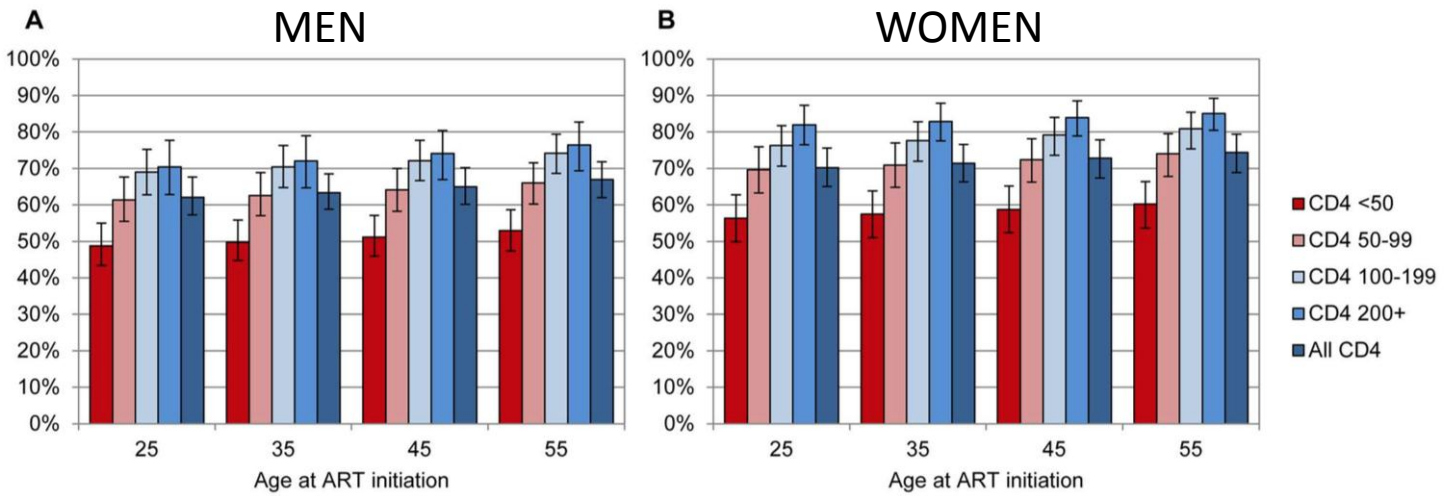
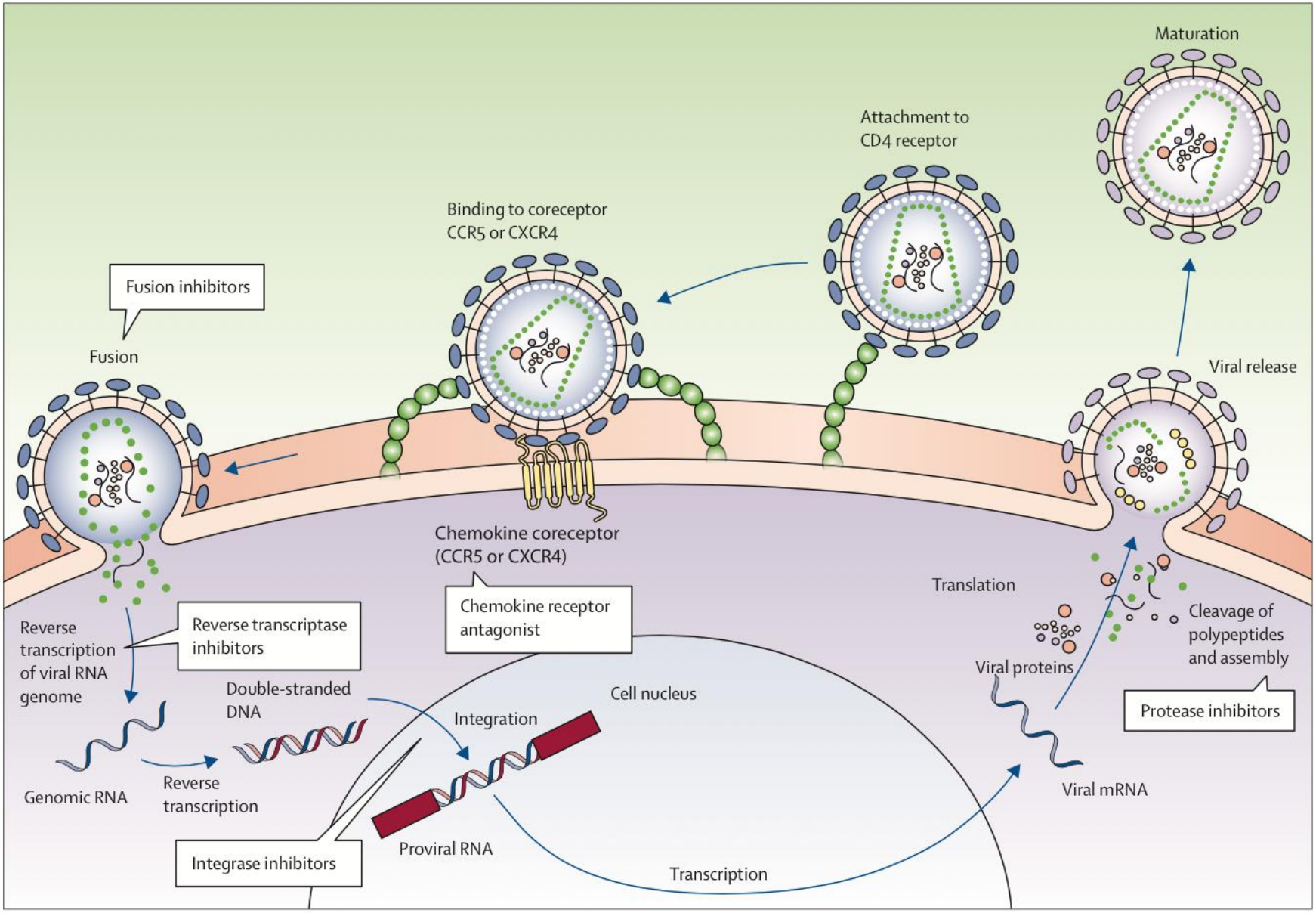


Figure 1. Life expectancies of patients starting ART, as proportions of life expectancies of HIV-negative adults. Proportions are plotted by age at ART initiation and baseline CD4 count, for men (A) and women (B). Bars represent means, and error bars represent 95% confidence intervals.
doi:10.1371/journal.pmed.1001418.g001

Johnson, 2013

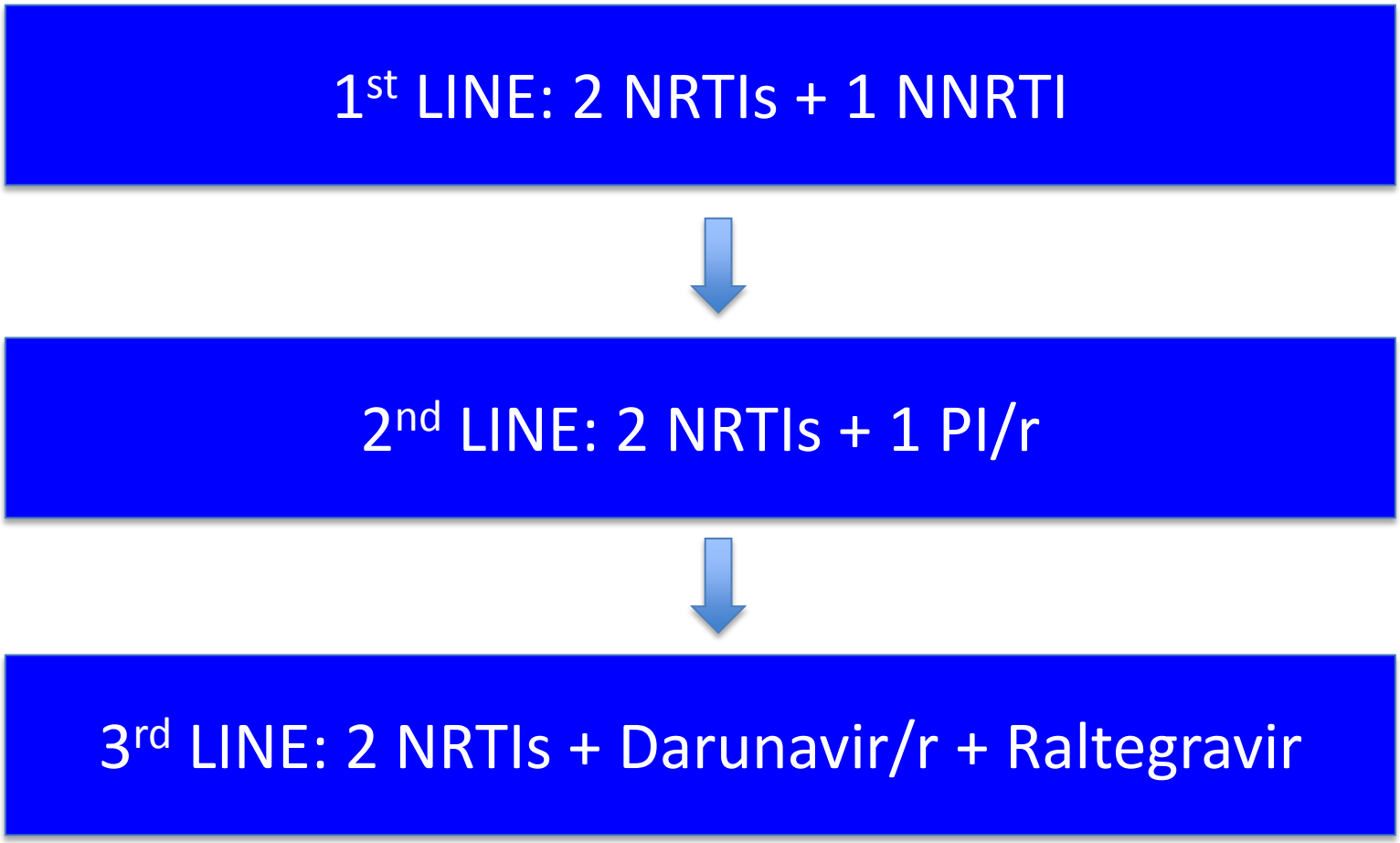


Maartens, Lancet 2014

ART drug classes

Class	Examples
Nucleos(t)ide reverse transcriptase inhibitors (NRTIs)	Zidovudine (AZT) Tenofovir (TDF)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (EFZ) Nevirapine (NVP)
Protease inhibitors (PIs)	Lopinavir/ritonavir (LPV/r) Darunavir/ritonavir (DRV/r)
Integrase strand transfer inhibitors (InSTIs)	Raltegravir Dolutegravir
CCR5 blockers	Maraviroc
Fusion inhibitors	Enfuvirtide

SA public sector: standardised regimens

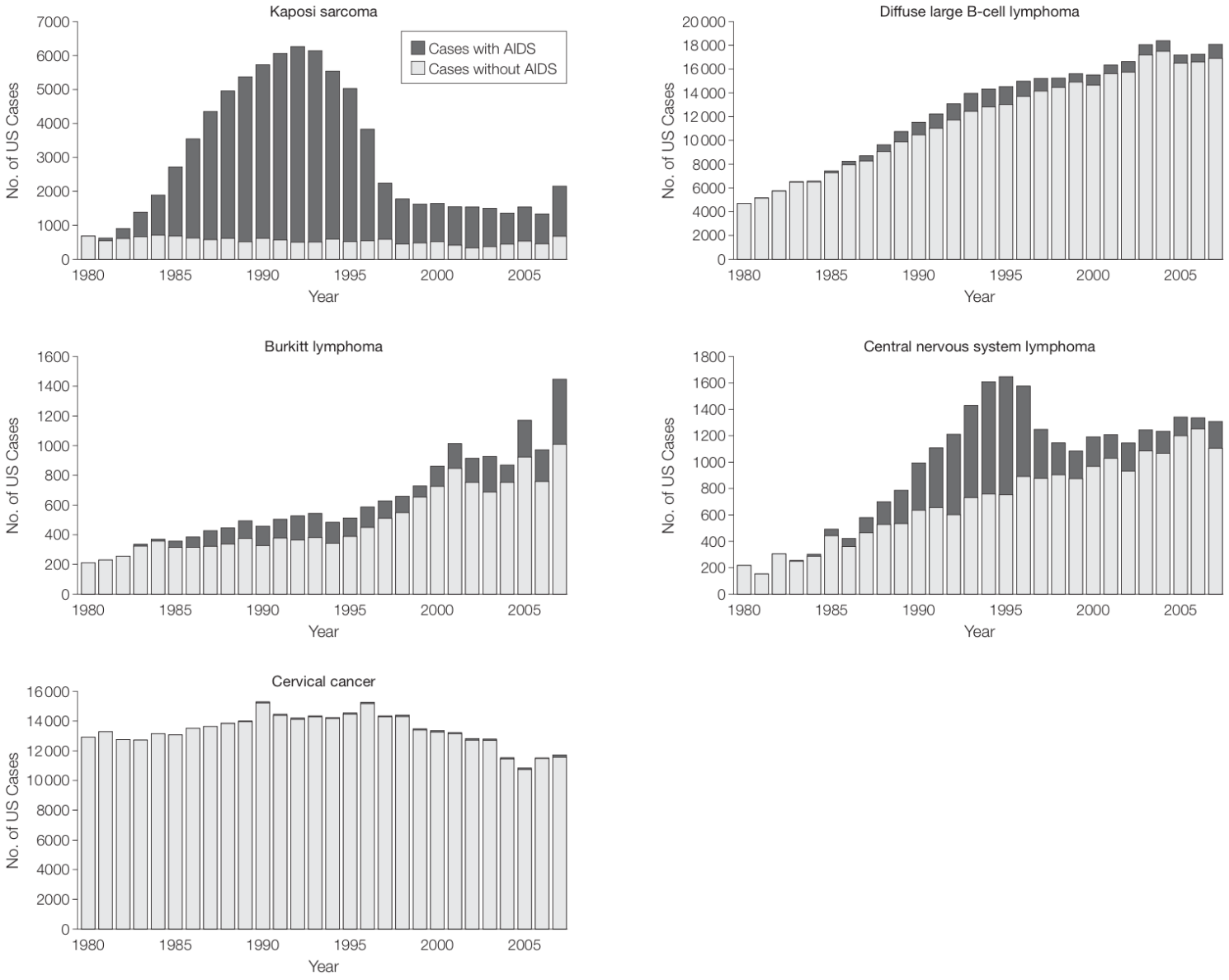


Indications for transplant in HIV

- Non-Hodgkin Lymphoma
  - Remains 22.6 x more frequent than in HIV-
- Hodgkin Lymphoma
  - No decrease in ART era
  - Remains 13.6 x more frequent than in HIV-
- Leukaemia
  - Certain studies have reported increased risk in HIV
- HIV-unrelated aetiologies

Engels, AIDS 2006
Shiels, JAIDS 2009

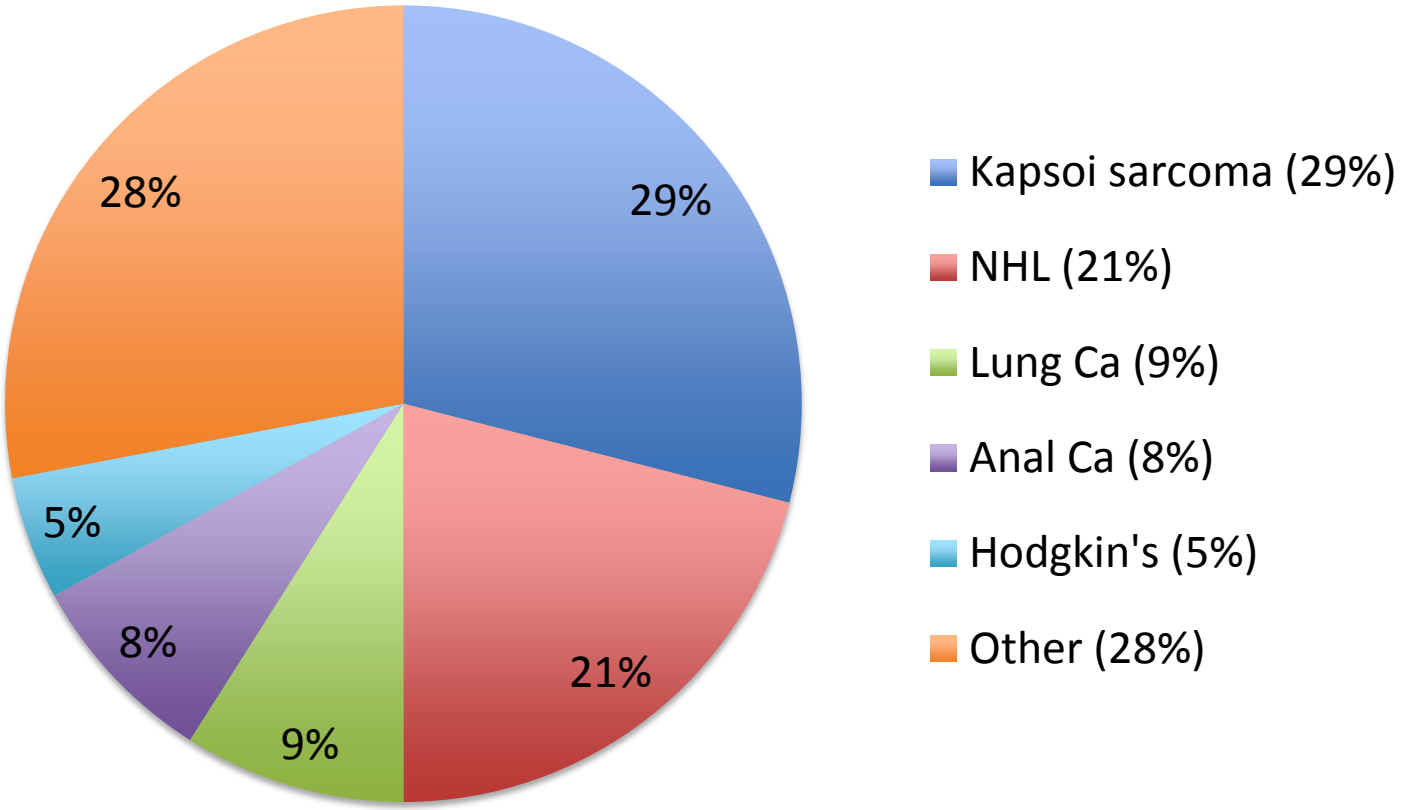
Figure 1. Number of AIDS-defining Cancer Cases in the United States in Persons With and Without AIDS by Calendar Year



Estimated counts of each malignancy that occurred among persons with and without AIDS in the United States by calendar year during 1980-2007.

Shiels, JAMA 2011

Incident cancer cases among HIV- infected adults treated with ART in the Centers for AIDS Research Network of Integrated Clinical Systems cohort from 1996 to 2009 (n=650)



Lymphoma accounted for 31% of cancer deaths

Achenbach, AIDS, 2011

Proportion of Burkitt's lymphoma increasing in ART era

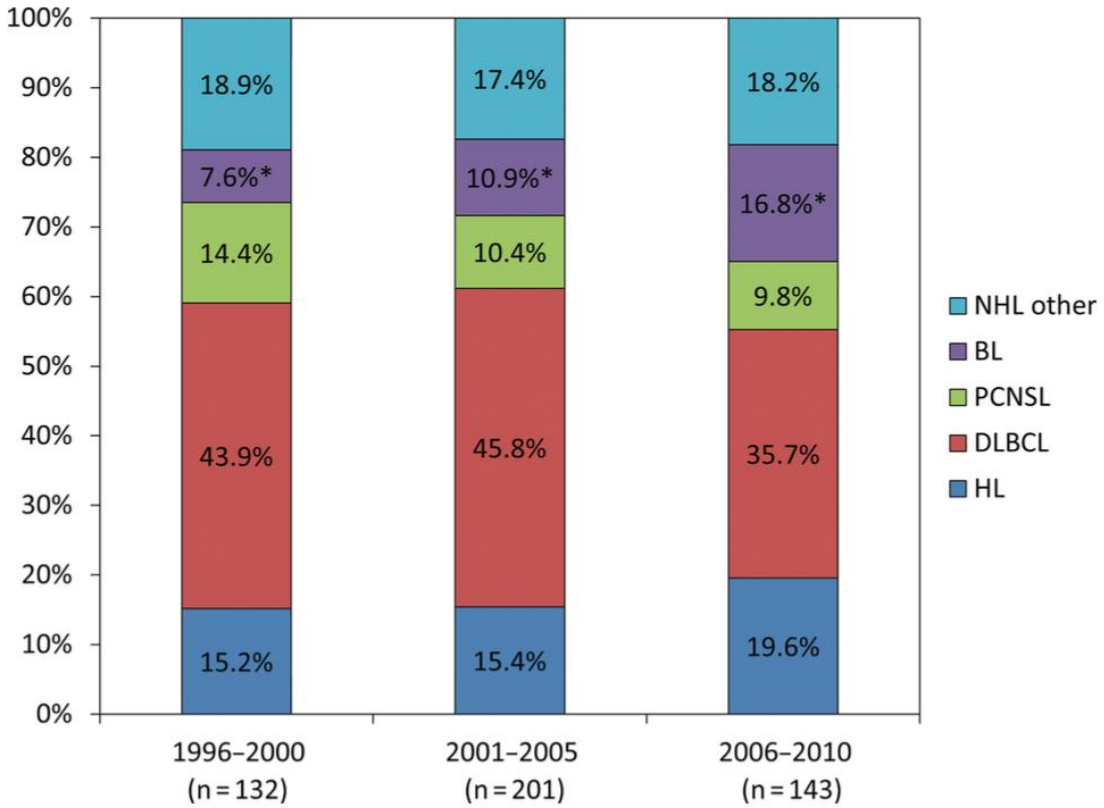


Figure 1. Proportional distribution of 476 HIV-associated lymphomas in the Center for AIDS Research Network of Integrated Clinical Systems cohort by lymphoma diagnosis year, 1996 to 2010. *Cochran–Armitage P_{trend} for Burkitt lymphoma (BL) proportion relative to diffuse large B-cell lymphoma (DLBCL) is .01, BL relative to primary central nervous system lymphoma (PCNSL) is .02, and BL relative to all non-BL Non-Hodgkin lymphoma (NHL) is .02. For all other pairwise comparisons between lymphoma categories, Cochran–Armitage P_{trend} is greater than .05. All reported statistical tests are two-sided. HL = Hodgkin lymphoma.

Gopal, JNCI 2013

HCT in HIV+ patients

- In patients who are virologically suppressed on ART, standard high dose regimes are appropriate
- Most experience with autologous PBSCT
- Concerns regarding immune reconstitution with allogeneic HCT

Survival and complications of HIV+ patients with Hodgkin lymphoma and NHL undergoing autologous SCT

Author	Year	Number HIV+	Overall survival (median follow-up)	SCT-related mortality	Infection-related mortality
PROSPECTIVE TRIALS					
Re	2003	16	60% (2-4 months)	0%	0%
Krishnan	2005	20	85% (32 months)	5%	0%
Serrano	2005	11	64% (28 months)	0%	9%
Spitzer	2008	20	74% (23 weeks)	5%	0%
CASE-CONTROL STUDIES					
Diez-Martin	2009	53	59% (30 months)	0%	8%
Krishnan	2010	29	75% (24 months)	0%	3%
Simonelli	2010	24	NR	NR	8%
RETROSPECTIVE STUDIES					
Gabarre	2004	14	36% (12 months)	0%	0%
Balsalobre	2009	68	61% (36 months)	NR	NR

Summarised in Echenique, Curr Infect Dis Rep 2014

blood
2009 113: 6011-6014
doi:10.1182/blood-2008-12-195388 originally published online March 23, 2009

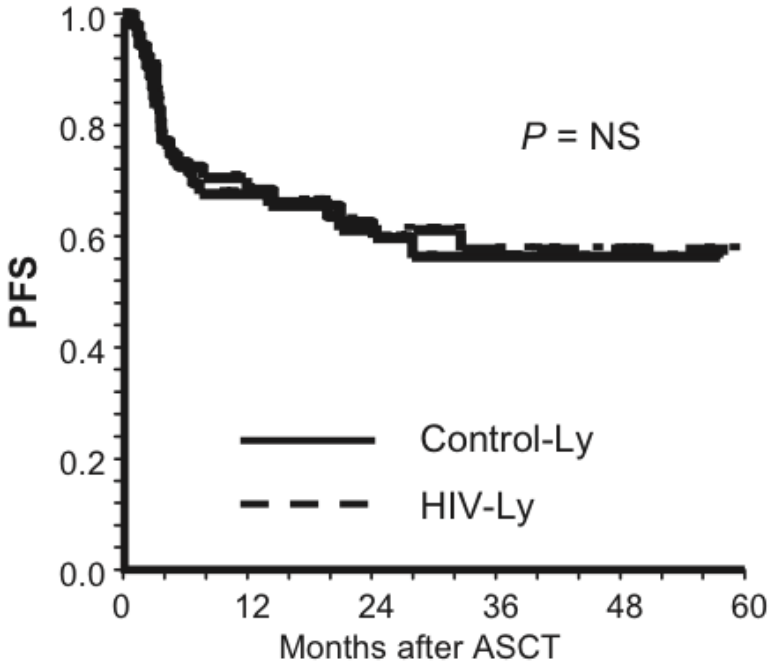
Comparable survival between HIV$^+$ and HIV$^-$ non-Hodgkin and Hodgkin lymphoma patients undergoing autologous peripheral blood stem cell transplantation

José L. Díez-Martín, Pascual Balsalobre, Alessandro Re, Mariagrazia Michieli, José M. Ribera, Carmen Canals, Eulogio Conde, Anne Rosselet, Ian Gabriel, Rosario Varela, Bernardino Allione, Kate Cwynarski, Philippe Genet, Ildefonso Espigado, Pierre Biron, Norbert Schmitz, Anne E. Hunter, Augustin Ferrant, Gaelle Guillerm, Mark Hentrich, Manuel Jurado, Pascual Fernández, David Serrano, Giuseppe Rossi and Anna Sureda

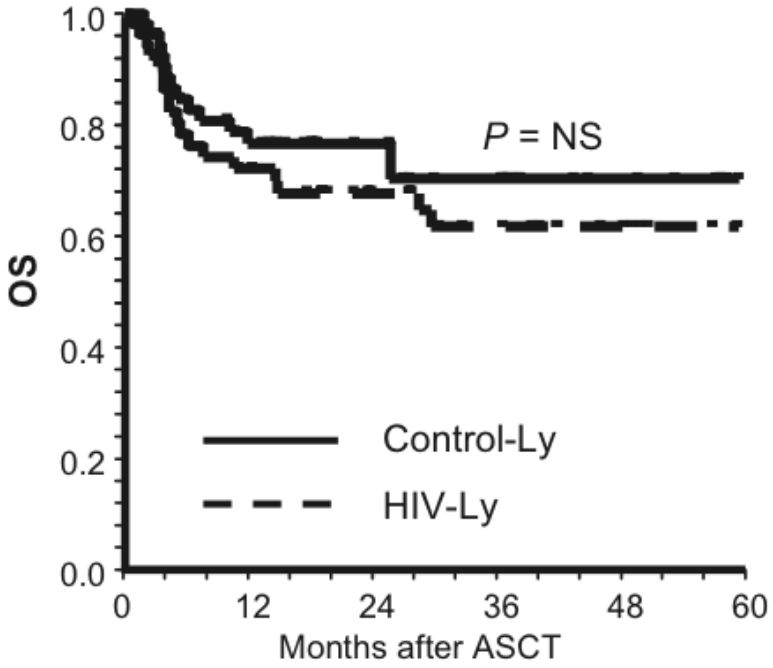
53 HIV+ vs 53 HIV-neg lymphoma patients

- Matched on several criteria
- 66% NHL; 34% Hodgkin in both groups
- 95% in HIV+ group received BEAM/variant
- 100% neutrophil engraftment in both

Progression-free survival



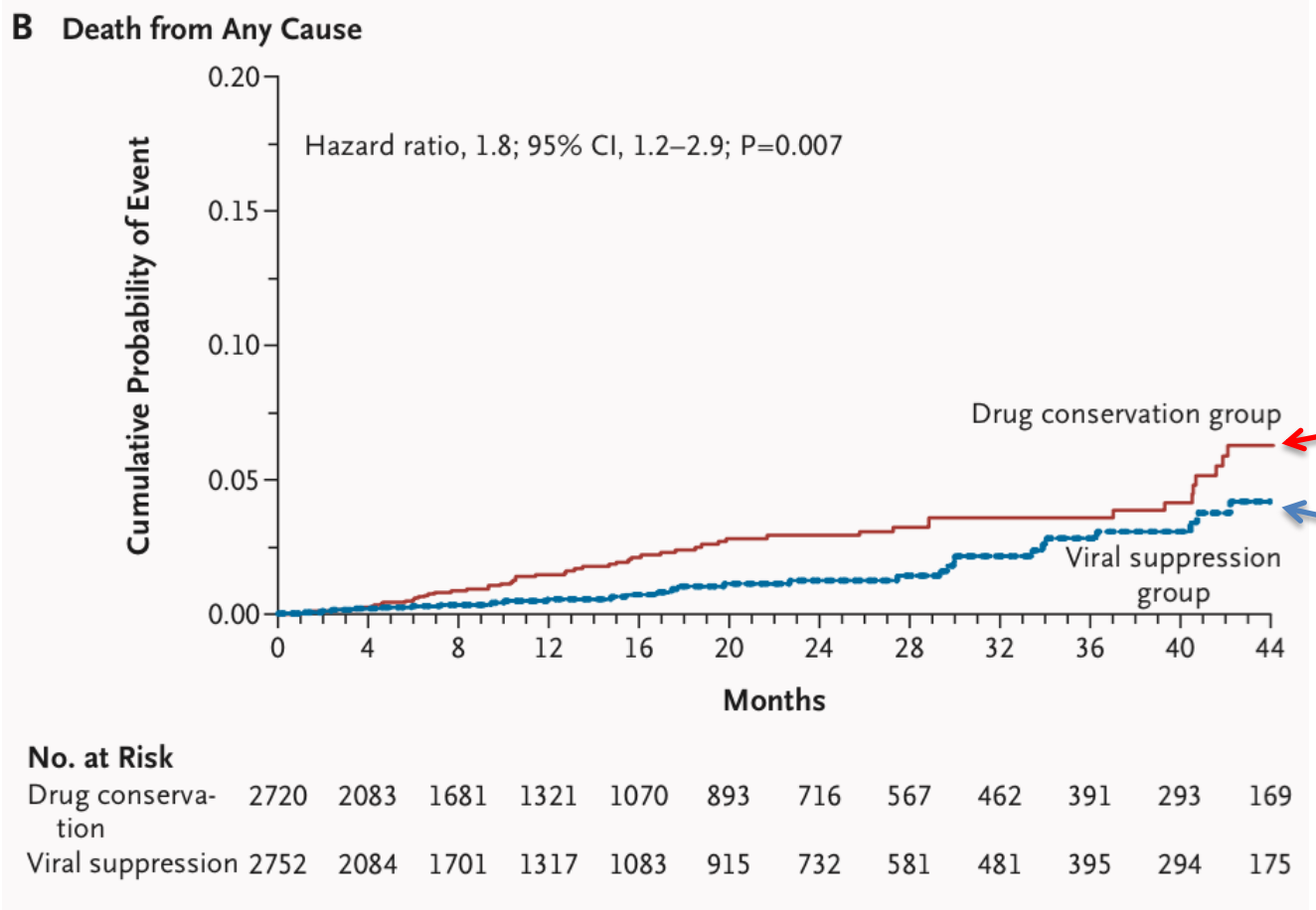
Overall survival



Generally ART should not be interrupted

- Reasons this is considered
  - Mucositis, nausea & vomiting, GIT dysfunction
  - Currently no injectable ART regimens
- ART syrups may be an option
- Interruptions may be associated with
  - Drop in CD4 count to nadir
  - Viral rebound with acute retroviral syndrome
  - ART resistance
- SMART trial
  - Interrupting ART associated with increased mortality

SMART randomised controlled trial



Interrupted ART

Continuous ART

El-Sadr, NEJM 2006

Association of early HIV viremia with mortality after HIV-associated lymphoma

Satish Gopal[a,*], Monita R. Patel[a,*], Elizabeth L. Yanik[a], Stephen R. Cole[a], Chad J. Achenbach[b], Sonia Napravnik[a], Greer A. Burkholder[c], Erin G. Reid[d], Benigno Rodriguez[e], Steven G. Deeks[f], Kenneth H. Mayer[g], Richard D. Moore[h], Mari M. Kitahata[i], Kristy L. Richards[a] and Joseph J. Eron[a]

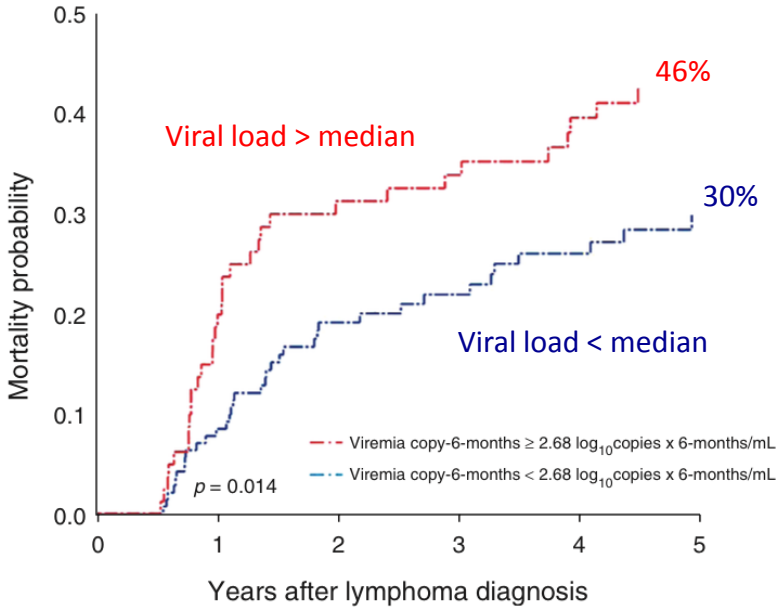


Fig. 2. Cumulative mortality after lymphoma diagnosis for 224 HIV-infected adults in Center for AIDS Research Network of Integrated Clinical Systems, stratified by HIV viremia copy-6-months (log_{10}copies × 6-months/ml).

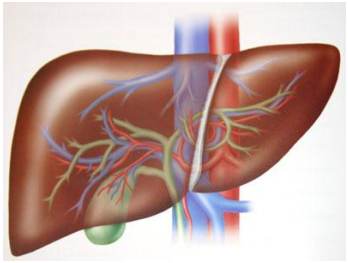
224 lymphoma patients
- 82% NHL
- 18% HL

"Exposure to each additional 1-unit log10 in HIV RNA throughout the 6 months after lymphoma diagnosis was associated with a 35% increase in subsequent mortality. These results suggest that early and effective ART during chemotherapy may improve survival."

Gopal, AIDS 2013

ART drug interactions

- Nevirapine
  - mainly 3A4
- Efavirenz
  - mainly 2B6
- Protease inhibitors
  - mainly 3A4



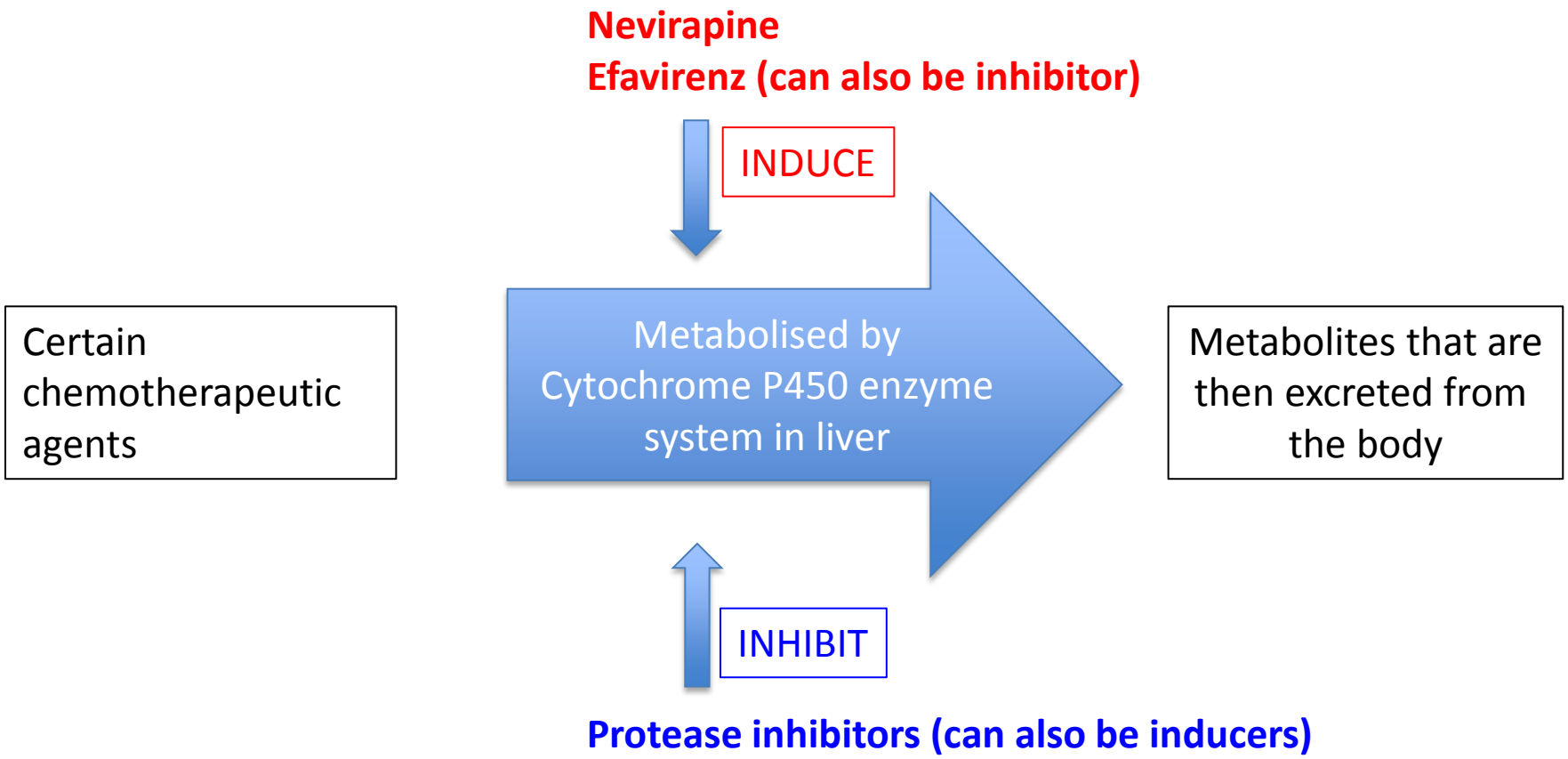
Metabolised by Cytochrome P450 enzyme system in liver

Metabolites that are then excreted from the body

NNRTI and PI concentrations are affected by CypP450 inducers and inhibitors

NRTIs and integrase inhibitors not metabolised through this enzyme system

ART drug interactions



The new NNRTI rilpivirine is not an inducer nor inhibitor of CypP450
The NRTIs and integrase inhibitors do not affect CypP450 metabolism

University of Liverpool
ART drug interactions website

www.hiv-druginteractions.org

Cyclophosphamide

- Conditioning regimens
- Metabolised through Cyp3A4
  - Levels ↑ with PIs - toxicity
  - Levels ↓ with NNRTIs – potentially subtherapeutic
- Potential risk of more infections with PIs
  - UK: More infections requiring hospitalisation in patients on PIs vs other ART, but no mortality difference [1]
  - US: No difference in any outcomes, PI vs non-PI ART [2]
- If possible use alternative non-PI ART during conditioning

1) Bower, J Clin Oncol 2005
2) Wong, Antivir Ther 2013

Cyclosporine/Tacrolimus

- Prevention and treatment of GVHD
- Metabolised through Cyp3A4
  - Levels ↑↑ with PIs - toxicity
  - Levels ↓↓ with NNRTIs – subtherapeutic
- Need to adjust dose/dose interval and perform intensive TDM to establish correct dose
- Experience in solid organ transplants suggests that finding optimal dose is possible but often very unorthodox doses required
  - eg. Low-dose tacrolimus once weekly with LPV/r (as low as 0.5mg/week [Muller, NEJM 2010])
- One approach is pre-transplant dose finding to establish optimal dose

Relevant short-term ART toxicities

Drug	Toxicities	Comment
Tenofovir	Nephrotoxicity	Avoid or switch if renal impairment
3TC / FTC	-	Well tolerated
Zidovudine	Anaemia Neutropaenia	Avoid in peri-transplant period
Abacavir	Hypersensitivity reaction	Rare in people of African descent
Stavudine/Didanosine	Neuropathy	Overlap with chemotherapy side effect
Nevirapine	Rash, hepatitis	
Efavirenz	Neuropsychiatric Hepatitis, rash	
Rilpivirine	Hepatitis, rash	
Protease inhibitors	GI intolerance, hepatitis	
Integrase inhibitors	Rash (rare)	Generally well tolerated

Tenofovir nephrotoxicity
Systematic review and meta-analysis

- 17 studies
  - 9 RCT
  - 8 Observational
- Tenofovir vs other regimens
  - Mean difference in calculated CrCl: -3.9 ml/min
  - Risk difference for acute renal failure: 0.7%
- But many studies exclude higher risk patients

Cooper, Clin Infect Dis 2010

Risk factors for tenofovir nephrotoxicity

- 35/744 (4.7%) on tenofovoir developed renal impairment

- Risk factors
  - Concurrent nephrotoxic medications
    - ACE inhibitors, NSAIDs, Amphotericin B
  - Medical comorbidities
  - Hypertension
  - Chronic pain
  - Concurrent and previous PI use
  - History of OI

Castellano, IAC 2008, WEAB0104

Tenofovir during HCT

- Not contra-indicated

- If renal function deteriorates in the context of sepsis or with other nephrotoxic agents may be necessary to switch to alternative
  - eg. Abacavir

Prophylaxis

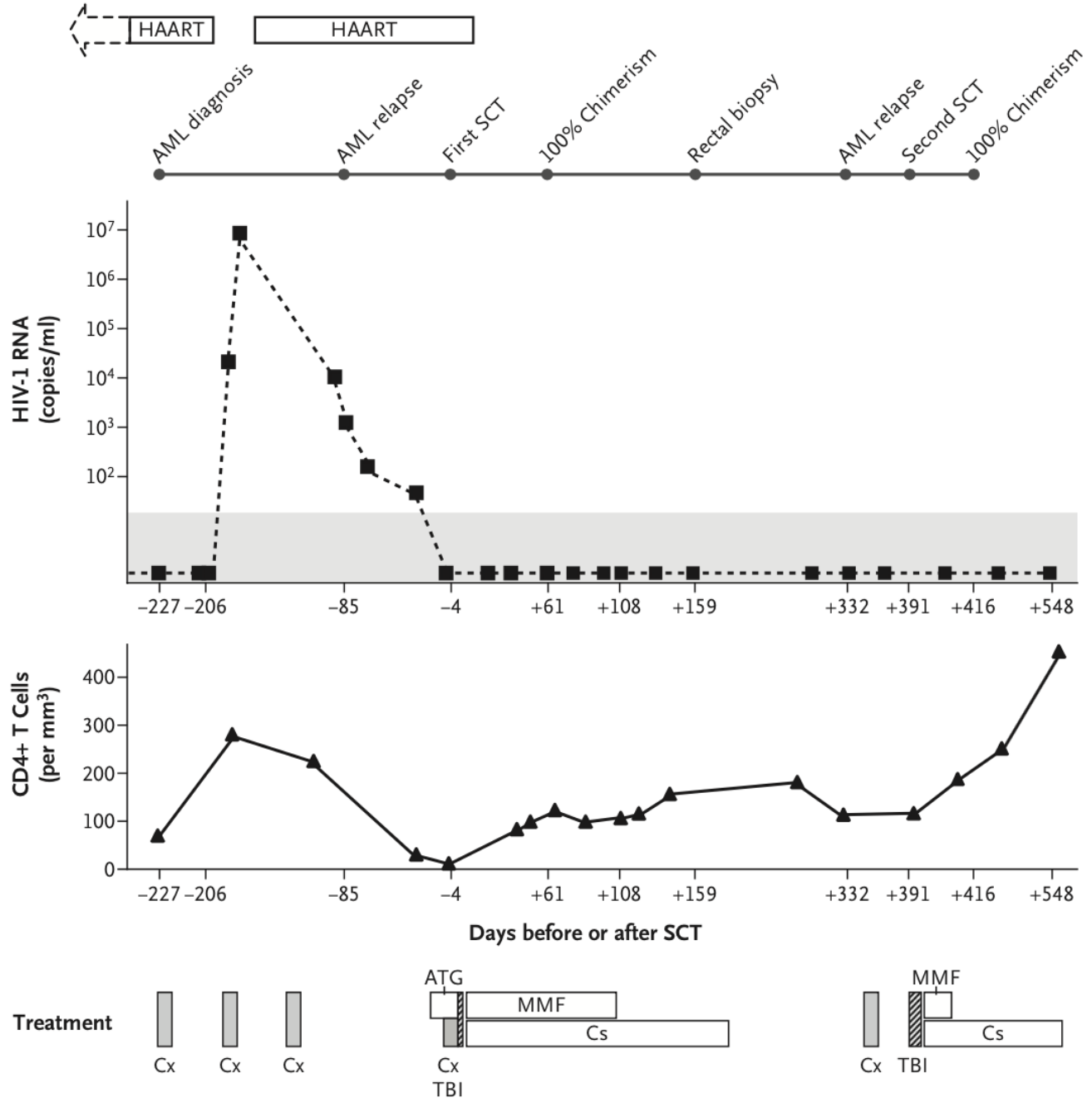
- Standard transplant prophylaxis regimens including co-trimoxazole

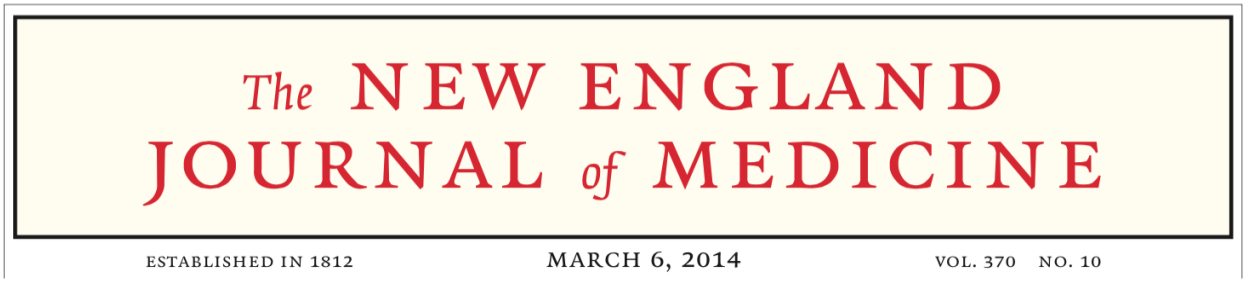
- INH prophylaxis is advised for HIV+ patients with positive tuberculin skin tests and all those on ART in high burden TB settings
  - In patient with lymphoma difficult to exclude active TB disease and hepatotoxicity a concern at time of HCT

HIV cure: the “Berlin patient”

- 40 year old HIV+ man on ART
- AML treated with induction and consolidation
- AML relapse 7 months after presentation
- 2 x allogeneic PBSCT from HLA-identical donor who was homozygous for *CCR5* delta32 allele
- Control of HIV-infection for more than 7 years without ART
  - No viral replication detected
  - No viral DNA in blood, marrow or rectal mucosal

Hutter, NEJM 2009


HAART
HAART
AML diagnosis
AML relapse
First SCT
100% Chimerism
Rectal biopsy
AML relapse
Second SCT
100% Chimerism
HIV-1 RNA (copies/ml)
10^7
10^6
10^5
10^4
10^3
10^2
−227 −206 −85 −4 +61 +108 +159 +332 +391 +416 +548
CD4+ T Cells (per mm³)
400
300
200
100
0
−227 −206 −85 −4 +61 +108 +159 +332 +391 +416 +548
Days before or after SCT
Treatment
Cx
Cx
Cx
ATG
MMF
Cs
Cx
TBI
MMF
Cs
Cx
TBI



Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

- Gene editing of autologous CD4 T cells (*CCR5* gene rendered permanently dysfunctional by a zinc-finger nuclease) then re-infused
- Safe in 12 patients (1 transfusion reaction)
- Modified cells had estimated mean half-life of 48 wk
  - Appeared to have survival advantage in patients interrupting ART

- Alternative approaches include infusions of autologous *CCR5*-modified hematopoietic stem cells
- Adequate engraftment and viral reservoir eradication required
  - Combining conditioning and "graft versus viral reservoir" responses

Tebas, NEJM 2014
Smily, Clin Infect Dis 2014

Conclusions

- ART has dramatically improved survival in HIV+ patients generally
- Autologous HCT outcomes in HIV+ patients on ART comparable to HIV-negative patients
- ART should generally be continued
- Important drug interactions especially protease inhibitors and cyclosporine/tacrolimus