THE IMPACT OF HIV INFECTION ON OVERALL SURVIVAL IN CHILDREN WITH HODGKIN LYMPHOMA IN SOUTH AFRICA

Geel J[1], Eyal K[2], Rowe B[3], Chirwa T[4], Omar F[5], Stones DK[6], Goga Y[7], Stefan C[8], Van Zyl A[9], Van Emmenes B[10], Wedi O[11], Vaithilingum M[12], Hendricks M[13]

[1]University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital; [2]University of Cape Town, Faculty of Economics; [3]University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital University of the Witwatersrand; [4]Division of Epidemiology and Biostatistics, School of Public Health, [5]University of Pretoria, Steve Biko Academic Hospital, [6]University of the Free State, Universitas Hospital, [7]University of Kwazulu-Natal, Inkosi Albert Luthuli Hospital, [8]University of Stellenbosch, Tygerberg Hospital, [9]University of Stellenbosch, Tygerberg Hospital, [10]Frere Hospital, [11]University of Limpopo, Polokwane-Mankweng Hospital Complex, [12]Netcare Parklands Hospital, [13]University of Cape Town, Red Cross War Memorial Children's Hospital

For the South African Children's Cancer Study Group

The authors declare no conflict of interest

Background

- Overview of Hodgkin lymphoma (HL) treatment in South Africa over ten years, in both private and state sector.
- HL represents 4.6% of all reported childhood malignancies in South Africa.
- Sub-analysis performed to look specifically at HIV positive patients.

Poor prognostic features of all patients with HL: multivariate analysis

Factor	p value Cox regression	Multivariate
Age > 10 years	p <0.05	
Stage III and IV	**p < 0.05**	**p = 0.006**
B symptoms	p = 0.001	
Histological subtype	NS	
OEPA-COPP and ABVD-ChlVPP	**p = 0.028**	**p = 0.020**
Under-resourced setting	p = 0.0278	
HIV disease	**p < 0.001**	**p = 0.018**

Background

- South Africa is home to the world's largest HIV epidemic, with 6.2 million people living with HIV (12.7% of SA population, 17% of all HIV positive people in the world).
- The national rollout of antiretroviral medication has improved survival of children with HIV.
- Dearth of data on HIV infected children with Hodgkin lymphoma.

Background

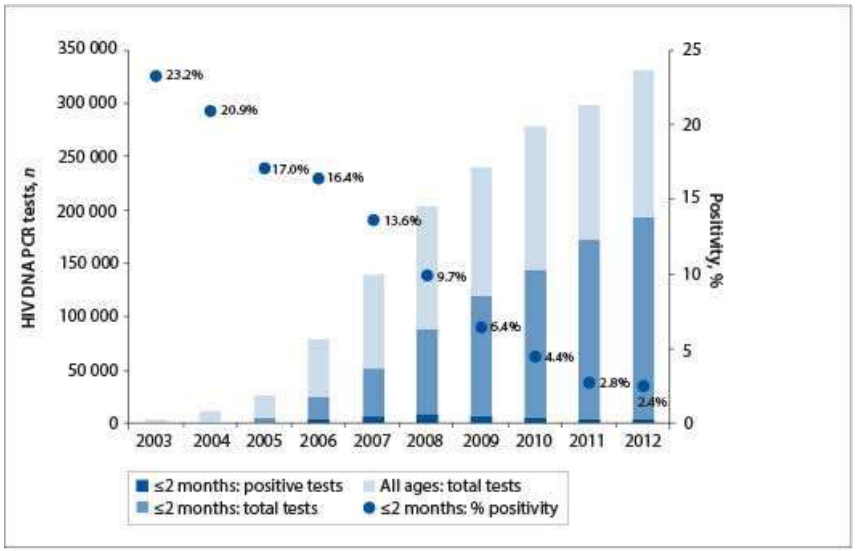


Fig. 1. Early vertical transmission in infants ≤2 months of age in South Africa. Illustration of the rapid scale-up of polymerase chain reaction (PCR) testing nationally with marked reduction in early vertical transmission of HIV over a decade. (KwaZulu-Natal data missing from 2003 to 2005.)

- Antiretroviral therapy national rollout initiated in April 2004.
- Low coverage rates in early years.
- Increased coverage as guidelines changed and access increased.
- Vertical transmission rate decreased from 22% to 2%.
- Coverage rate approximately 60%.
- Universal test and treat 1 Sept 2016.

Outcomes of HIV-associated Hodgkin lymphoma in the era of antiretroviral therapy

Adam J. Olszewski[a,b] and Jorge J. Castillo[c]

Objectives: Clinical series suggest favorable outcomes of HIV-associated Hodgkin lymphoma, in conflict with population-based statistics. Our objective was to investigate the proportion of Americans who received curative chemotherapy for this disease, and compare their survival with HIV-negative cases using population data.

Methods: We selected cases of HIV-associated Hodgkin lymphoma diagnosed in 2004–2012 from the National Cancer Data Base. Factors associated with receipt of chemotherapy were analyzed by logistic regression. Overall survival was compared in proportional hazard models adjusting for available confounding factors.

Results: Among 2090 HIV-positive patients, 81% received chemotherapy, but 16% received no treatment. Advanced age, male sex, nonwhite race, poor socioeconomic status, and undetermined histologic subtype were associated with higher risk of nontreatment. In 2012, 49% of HIV-positive patients were black, and 15% were Hispanic. Unadjusted 5-year overall survival was significantly lower for HIV-positive (66%) than for HIV-negative (80%) populations. However, among patients who received chemotherapy, HIV-positive status was not significantly associated with higher mortality in classical histologic subtypes, including nodular sclerosis (hazard ratio, HR, 1.08; 95% confidence interval, CI, 0.88–1.33) and mixed cellularity (HR, 1.06; 95% CI, 0.80–1.40). In contrast, prognosis remained significantly worse for cases with undetermined histology (HR, 1.56; 95% CI, 1.31–1.85), suggesting a more aggressive biology or other high-risk characteristics in this subgroup.

Conclusion: Worse survival statistics for HIV-associated Hodgkin lymphoma are driven by lower rates of chemotherapy administration. The disparity in treatment delivery needs attention because a majority of HIV-positive Americans with Hodgkin lymphoma are now black or Hispanic, and this proportion is increasing.

AIDS 2016, **30**:787–796

- Adults, USA
- OS for HIV positive group 66%
- HIV not a risk factor with classical HL.

High Risk Features Contrast With Favorable Outcomes in HIV-associated Hodgkin Lymphoma in the Modern cART Era, ANRS CO16 LYMPHOVIR Cohort

Caroline Besson,[1,2] Remi Lancar,[3,4] Sophie Prevot,[1,5] Pauline Brice,[6] Marie-Caroline Meyohas,[7] Bruno Marchou,[8] Jean Gabarre,[9] Fabrice Bonnet,[10] Cécile Goujard,[1,2] Olivier Lambotte,[1,2] François Boué,[1,11] Nicolas Mounier,[12] Marialuisa Partisani,[13] Francois Raffi,[14] Régis Costello,[15] Houria Hendel-Chavez,[1] Michele Algarte-Genin,[3,4] Selma Trabelsi,[3,4] Lucie Marchand,[16] Martine Raphael,[1] Yassine Taoufik,[1,17] and Dominique Costagliola[3,4]

[1]Université Paris Sud, Faculté de médecine Paris Sud, Le Kremlin-Bicêtre, [2]AP-HP, Hôpitaux Paris Sud, Service d'hématologie, Le Kremlin-Bicêtre, [3]Sorbonne Universités, UPMC Univ Paris 06, and [4]INSERM, UMR_S 1136, Institut Pierre Louis d'épidémiologie et de Santé Publique, Paris, [5]AP-HP, Hôpitaux Paris Sud Site Bêclère, Service d'anatomo-pathologie, Clamart, [6]Department of Hemato-oncology, Hôpital Saint-Louis, AP-HP, [7]AP-HP CHU Saint-Antoine, Service de maladies infectieuses, Paris, [8]CHU Toulouse, Service de maladies infectieuses, [9]AP-HP, CHU Pitié-Salpêtrière, Service d'hématologie, Paris, [10]CHU Bordeaux, Service de Médecine Interne et Maladies Infectieuses, and INSERM U593, Université de Bordeaux, [11]AP-HP, Hôpitaux Paris Sud Site Bêclère, Service d'immunologie clinique, Clamart, [12]Department of Onco-Hematology, Archet Hospital, Nice, [13]Hôpitaux Universitaires, Centre de soins de l'infection VIH, Strasbourg, [14]CMIT, Paris, [15]Department of Hematology, Hôpital La Conception, Marseille, [16]ANRS, Paris, and [17]AP-HP, Hôpitaux Paris Sud, Service d'immunologie biologique, Le Kremlin-Bicêtre, France

Background. Human immunodeficiency virus (HIV) infection is associated with a high risk of classical Hodgkin's lymphoma (cHL) in the combined antiretroviral therapy (cART) era.

Methods. We analyzed the characteristics and outcome of HIV-associated cHL diagnosed in the modern cART era. The French ANRS-CO16 Lymphovir cohort enrolled 159 HIV-positive patients with lymphoma, including 68 (43%) with cHL. HIV-HL patients were compared with a series of non-HV-infected patients consecutively diagnosed with HL.

Results. Most patients (76%) had Ann-Arbor stages III-IV and 96% of patients were treated with ABVD. At diagnosis, median CD4 T-cell count was 387/μL and 94% of patients were treated with cART. All patients received cART after diagnosis. Five patients died from early progression (n − 2), sepsis (1) or after relapse (2). Two additional patients relapsed during follow-up. Two-year overall and progression free survivals (PFS) were 94% [95% CI, 89%, 100%] and 89% [82%, 97%], respectively. The only factor associated with progression or death was age with a relative risk of 8.1 [1.0; 67.0] above 45 years. The PFS of Lymphovir patients appeared similar to PFS of HIV-negative patients, 86% [82%, 90%], but patients with HIV infection displayed higher risk features than HIV-negative patients.

Conclusions. Although high-risk features still predominate in HIV-HL, the prognosis of these patients, treated with cART and mainly ABVD, has markedly improved in the modern cART era and is now similar to non-HIV-infected patients.

- Most Stage III and IV
- 2 year OS 94% and PFS 89%
- 94% of the patients were on HIV therapy.
- Median CD4 count of 387 cells/mm^3
- OS of HIV positive cohort approached that of HIV negative cohort.

Known prognostic factors in HL

- Age
- Stage
- B symptoms
- Histological subtype
- Presence of bulky disease
- Response to chemotherapy
- Others…

Objectives

Primary objectives:

- Five year OS of HIV infected children.
- Compare with five year OS of whole cohort.

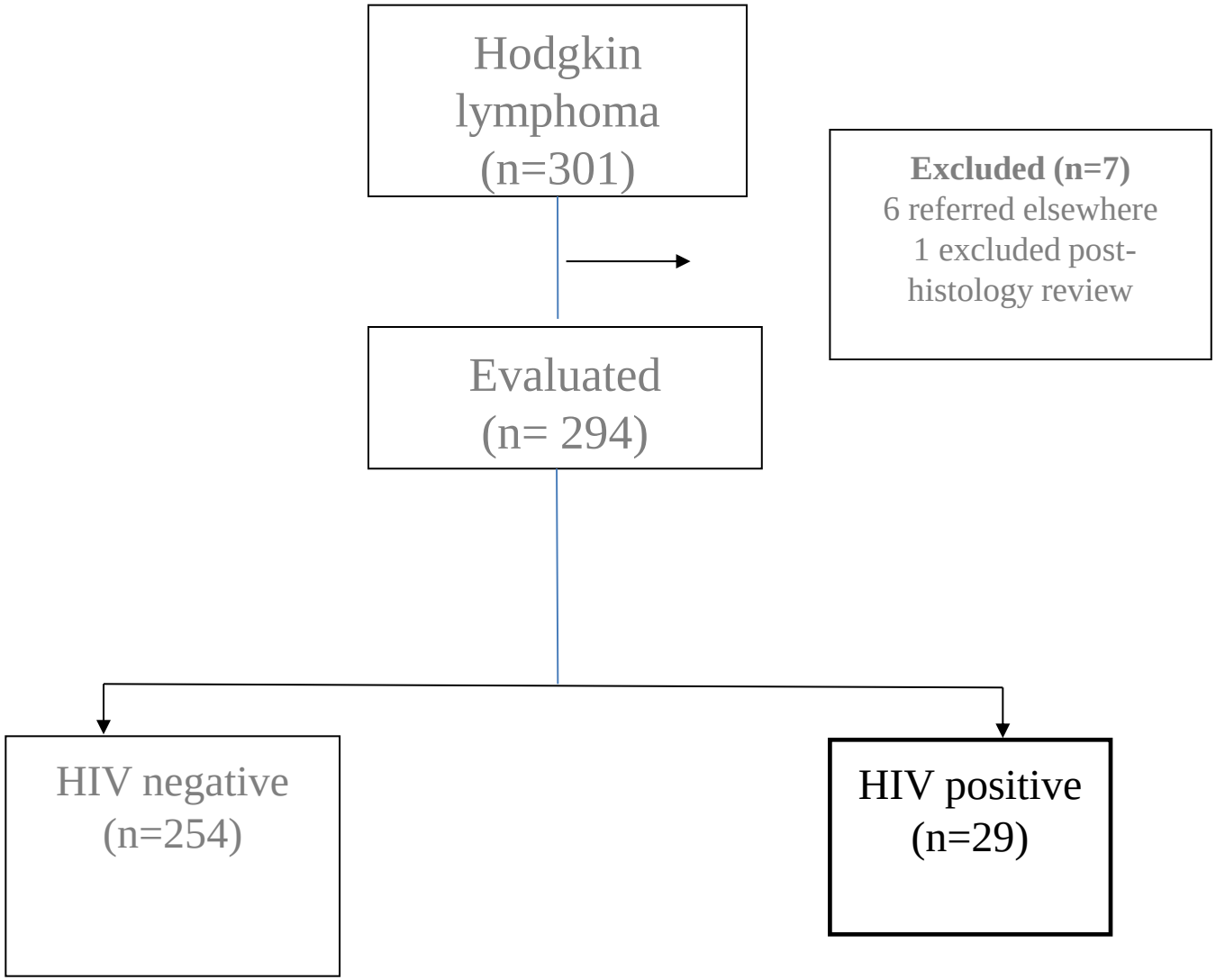
Secondary Objectives:

- Identify poor prognostic factors in HIV positive group if possible.
- Document causes of death.

Develop hypotheses to guide prospective study.

Methods

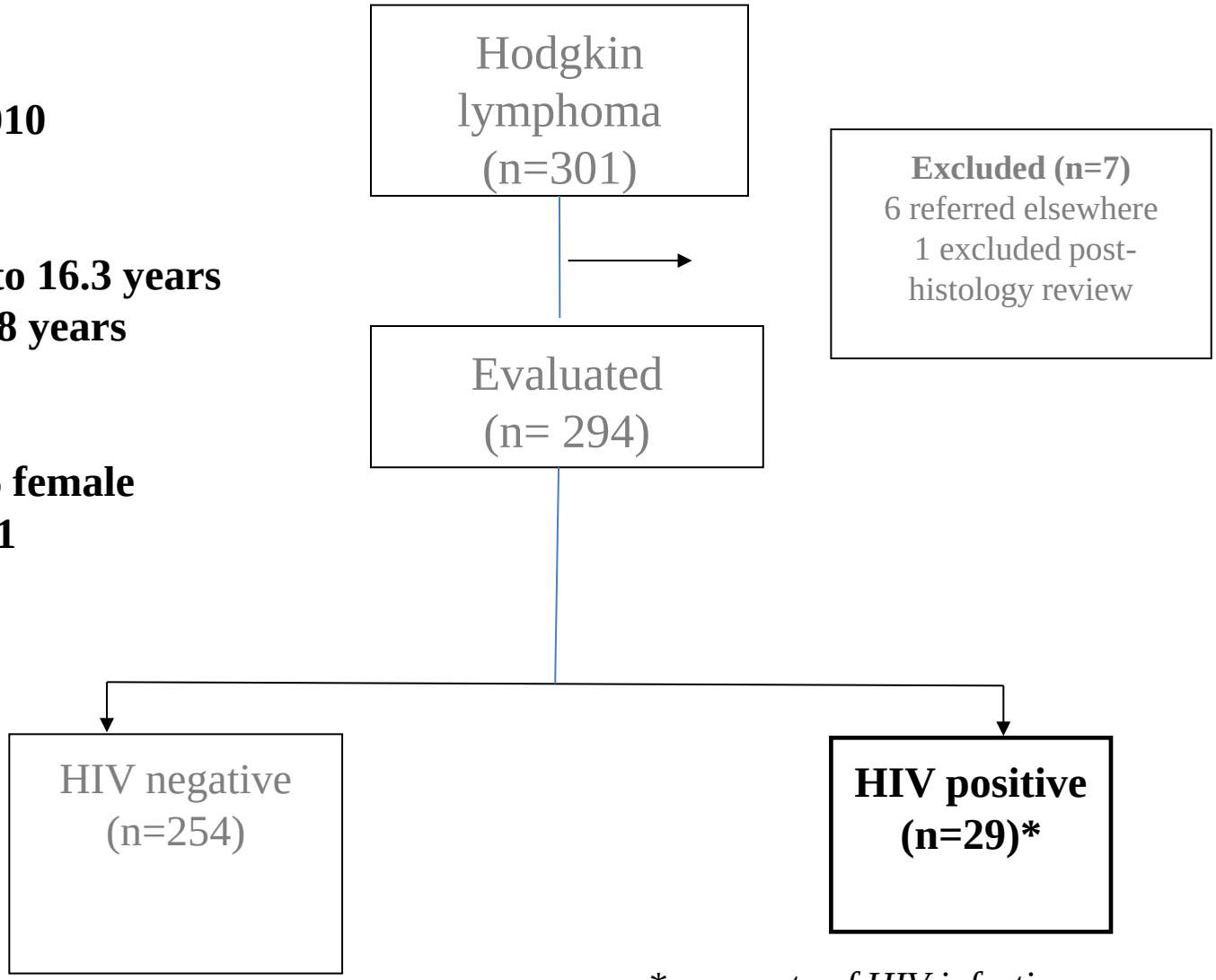
- A retrospective study was conducted to determine survival rates and prognostic factors in South African children with HL, and a sub-analysis was performed of children with HIV.
- Descriptive statistical methods.
- Kaplan-Meier survival curves.
- Cox regression model for prognostic factors.
- Pearson’s Chi square test for differences between groups.


Hodgkin lymphoma (n=301)
Excluded (n=7)
6 referred elsewhere
1 excluded post-histology review
Evaluated (n= 294)
HIV negative (n=254)
HIV positive (n=29)

Duration:
2000 to 2010

Age:
3.3 years to 16.3 years
median 6.8 years

Sex:
23 male, 6 female
ratio 3.8: 1



**same rate of HIV infection as paediatric population during study period*

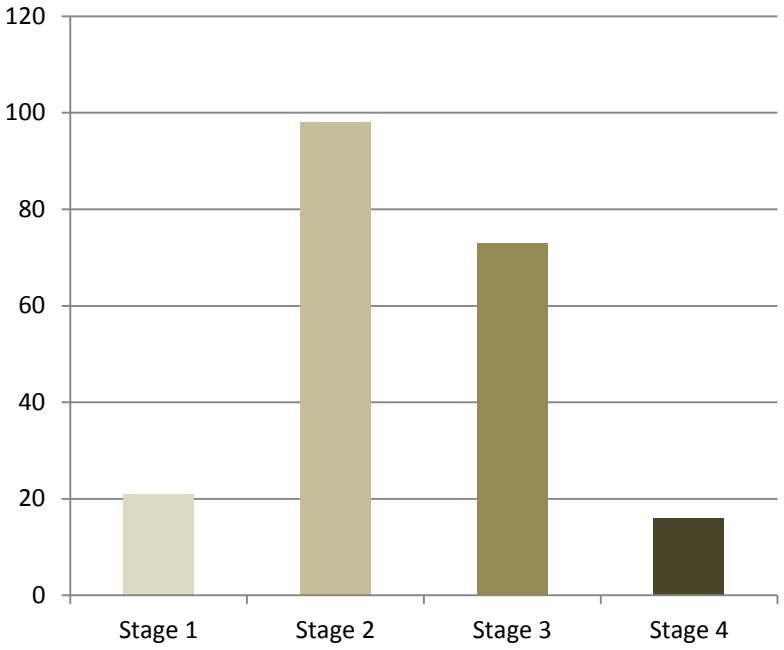
HIV disease characteristics

WHO immunological stage data not available

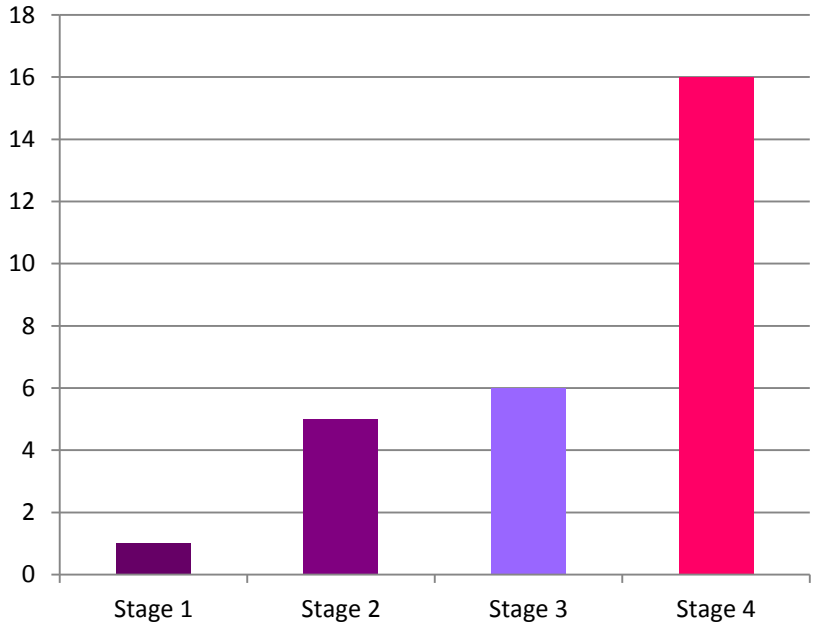
- CD4 % (n = 24)
  - Range 2.4% to 45% (normal > 25%)
  - Median 18.3
- ABSOLUTE CD4 counts (n = 24)
  - Range <1 to 1441
  - Median 353
- HIV Viral load (n = 17)
  - Range undetectable to 656 000 (log 5)
- Antiretroviral therapy
  - 9/29 on ARV at time of diagnosis of HL
  - 7/9 virally suppressed

Ann Arbor stage of HL

HIV negative children



HIV positive children



Significant difference between early and late stage patients
p = 0.0029

HL Disease characteristics

	HIV positive N = 29	%	HIV negative N = 254	%	Pearson's chi square
HISTOLOGICAL SUBTYPE					
Nodular sclerosing	5	**17.2**	115	**45.3**	
Mixed cellularity	16	**55.2**	101	**39.8**	
Lymphocyte depleted	2	**6.9**	9	**3.5**	
Nodular lymphocyte predominant	2	**6.9**	6	**2.4**	
Interfollicular	0	**0**	2	**0.8**	
Unclassified	5	**17.2**	21	**8.3**	
B SYMPTOMS					
Yes	20	**70**	150	**59.1**	p = 0.18
No	9	**30**	102	**40**	
BULKY DISEASE					
Yes	10	**34.5**	99	**39**	p = 0.86
No	19	**65.5**	154	**60.6**	

Nutritional status

- Nutritional assessment by registered dietician.
- Parameters included height, weight, BMI, albumin, phosphate, potassium.
- N = 29, some data missing.
- Majority in catabolic state with decreased nutrient absorption.

Parameter	↑	N	↓
Height for age	**1**	**10**	**17**
Weight for age	**1**	**17**	**11**
BMI for age	**0**	**27**	**2**
Protein catabolism	**16**	**4**	**0**
Nutrient absorption	**0**	**11**	**17**

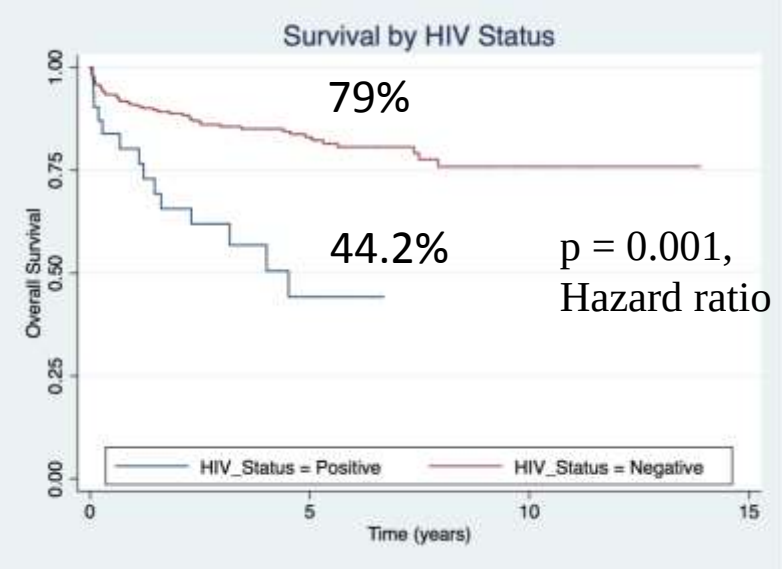
Recognised chemotherapy protocols for HL in South Africa

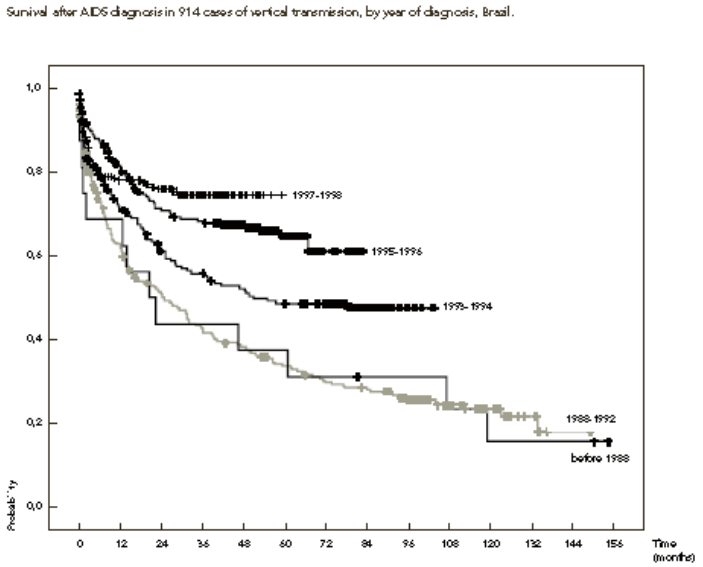
1.	OPPA/OEPA-COPP	9 pt / 97 total	(9.3%)
2.	ABVD	17 pt / 158 total	(10.8%)
3.	ABVD-ChlVVP	1 pt / 31 total	(3.2%)

- Patients not enrolled in prospective trials.
- Chemotherapy regimens chosen according to institutional preference.

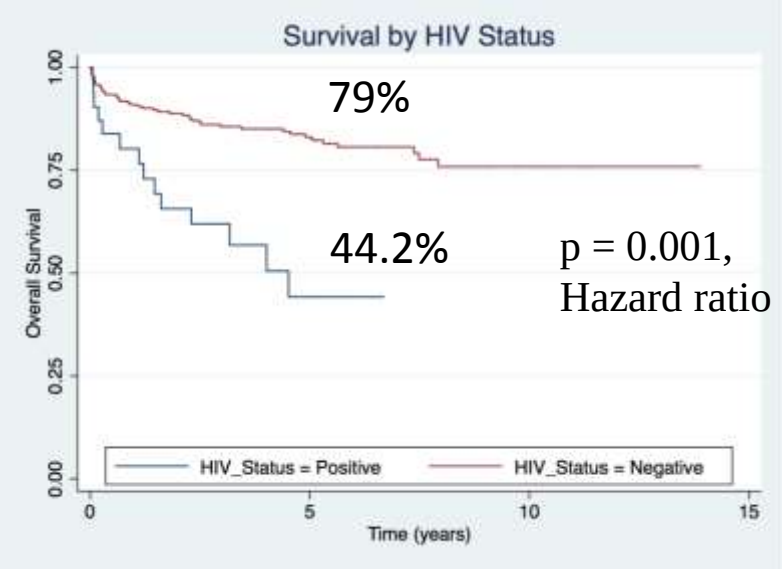
- Same protocols used for HIV positive and negative patients. Dose modifications on patient-by-patient basis.
- ARVs started as soon as possible. TB treated if diagnosed. (4/29 = 13.8%)
- 2 died before chemo could be started.
- 1 did not receive any chemo – nLPHD resected.

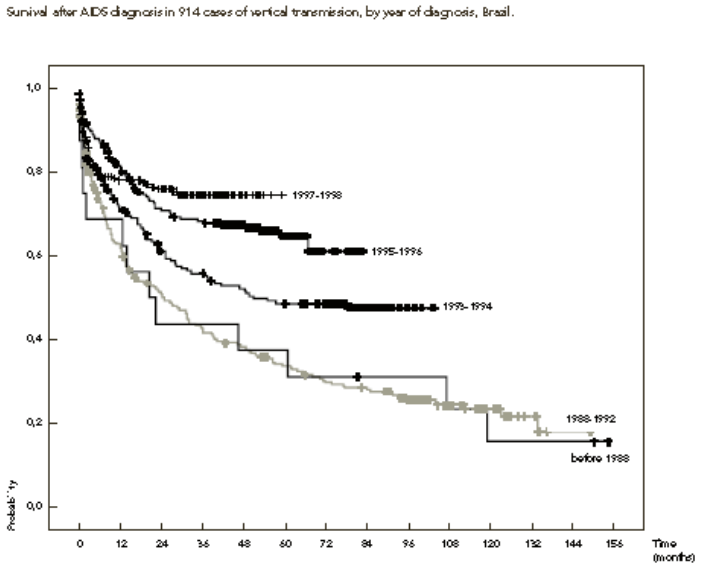
Overall survival





Overall survival





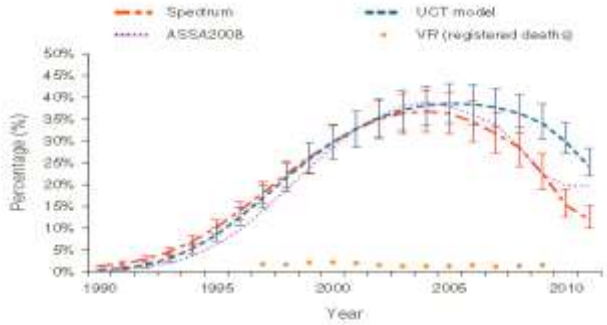


Fig. 1. Trend in percentage of under-five deaths in South Africa due to AIDS in South Africa. ASSA, Actuarial Society of South Africa; UCT, University of Cape Town; VR, vital registration.

Potential prognostic factors in HIV positive children

Factor	Log rank comparison of survival curves
Bulky disease	P = 0.90
B symptoms	**P = 0.03**
CD4 percent (<15%)	**P = 0.005**
On ARVs at time of diagnosis of HL	P = 0.10
Stage of HL	P = 0.52
Viral suppression at diagnosis of HL	P = 0.74
Malnutrition Underweight Increased protein catabolism	 P = 0.95 P = 0.59
Age > 10 years	P = 0.35

Causes of death

Cause of death	HIV positive		HIV negative	
Relapse/ refractory disease	7/ 14	(50%)	35/45	(78%)
Infection • Pneumonia, septicaemia • Neutropaenic sepsis: *Acinetobacter baumanii* • Varicella, *Streptococcus pneumoniae* • MRSA • PCP, IRIS	**6/14**	**(43%)**	7/45	(16%)
Undocumented / Unknown	0/14	(0%)	2/45	(4%)
Second malignant neoplasm	1/14	(7%)	1/45	(2%)

Conclusions

- HIV prevalence rate in this HL population was the same as that of the South African paediatric population during the same period.
- In the HIV positive population, only an AIDS-defining CD4 count and B symptoms were found to have a significant impact on survival, although numbers were small.
- Predominance of poor prognosis histological subtypes but not significant.
- Children with HIV have a much higher chance of dying if diagnosed with HL than their HIV negative counterparts: causes of death include infections and relapsed/refractory disease.
- This retrospective study represents the largest number of HIV positive children with HL reported, but there is not yet enough data to achieve statistical significance and it would be necessary to enrol more patients prospectively in a multicentre study across various countries with similar conditions to accurately determine reasons for poor outcomes.

References

1. http://www.statssa.gov.za/publications/P0302/P03022016.pdf
2. Stefan DC, Stones DK, Wainwright D, Kruger M, Davidson A, Poole J, Hadley GP, Forman D, Colombet M, Steliarova-Foucher E. Childhood cancer incidence in South Africa, 1987 – 2007. S Afr Med J. 2015 Oct 10;105(11):939-47.
3. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, Smith FO, Reaman GH. Outcomes for Children and Adolescents With Cancer: Challenges for the Twenty-First Century. *J Clin Oncol* 2010;28(15)2625-2634.
4. Bekker LG, Venter F, Cohen K, Goemare E, Van Cutsem G, Boulle A, Wood R. Provision of antiretroviral therapy in South Africa: the nuts and bolts. Antivir Ther. 2014;19 Suppl 3:105-16. doi: 10.3851/IMP2905. Epub 2014 Oct 13.
5. Stein L, Urban ML, O'Connell D *et al*. The spectrum of human immunodeficiency virus-associated cancers in a South African black population: Results from a case-control study, 1995 – 2004. *Int J Cancer 2008*;122:2260-2265.
6. Davidson A, Wainwright RD, Stones DK, Kruger M, Hendricks M, Geel J, Poole J, Reynders D, Omar F, Mathew R, Stefan DC. Malignancies in South African Children with HIV. *J Pediatr Hematol Oncol* 2014;36(2);111-117.
7. Stefan DC, Wessels G, Poole J, Wainwright L, Stones D, Johnston WT, Newton R.. Infection with human immunodeficiency virus-1 (HIV) among children with cancer in South Africa. *Pediatr Blood Cancer*. 201[illegible] Jan;56(1):77-9.

References

8. Mutalima N1, Molyneux EM, Johnston WT, Jaffe HW, Kamiza S, Borgstein E, Mkandawire N, Liomba GN, Batumba M, Carpenter LM, Newton R.. Impact of infection with human immunodeficiency virus-1 (HIV) on the risk of cancer among children in Malawi - preliminary findings. *Infect Agent Cancer.* 2010 Feb 12;5:5.
9. Besson C et al. High risk features contrast with favorable outcomes in HIV-associated Hodgkin Lymphoma in the modern cART era, ANRS CO16 LYMPHOVIR cohort. Clin Infect Dis. (2015) 61 (**9**): 1469-1475.
10. Olszwenski, A; Castillo, J. Outcomes of HIV-associated Hodgkin lymphoma in the era of antiretroviral therapy. AIDS 2016 Mar 13;30(5):787-96.
11. Birnbaum,JK, Murraya CJL, Lozanoa R. Exposing misclassified HIV/AIDS deaths in South Africa. *Bull World Health Organ* 2011;89:278–285 | doi:10.2471
12. Matida LH, Ramos Jr AN, Moncau JE, Marcopito LF, Marques HH, Succi RC, Della Negra M, Hearst N; Grupo Brasileiro de Estudo da Sobrevida em Crianças com AIDS. AIDS by mother-to-child transmission: survival analysis of cases followed from 1983 to 2002 in different regions of Brazil. Cad Saude Publica. 2007;23 Suppl 3:S435-44.

Thanks and acknowledgments

Mrs Ann Vorster, Colleges of Medicine

Dr Anita Gildenhuys, National Health Laboratory Services, Division of Anatomical Pathology, University of Witwatersrand

Ms Judy Schoeman, School of Dietetics, Steve Biko Academic Hospital

Organisers and sponsors of SIOP 2016

SPONSORS:

CANSA

Roche

Circle of Friends

jennifer.a.geel@gmail.com

jennifer.geel@wits.a.c.za