Published in final edited form as:

J Acquir Immune Defic Syndr. 2015 July 1; 69(3): e117–e118. doi:10.1097/QAI.0000000000000648.

Nationwide Study of Cancer in HIV-infected Taiwanese Children in 1998–2009

Marcelo Chen, MD, PhD^{1,2,3}, I-An Jen, MD, MS^{3,4}, and Yi-Ming Arthur Chen, MD, ScD^{3,5}

¹Department of Urology, Mackay Memorial Hospital, Taipei, Taiwan

²Department of Cosmetic Applications and Management, Mackay Junior College of Medicine, Nursing and Management, Taipei City, Taiwan

³Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan

⁴Department and Institute of Public Health, National Yang-Ming University, Taipei, Taiwan

⁵Department of Microbiology and Institute of Medical Research, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

To the Editors

We previously reported an increased incidence of cancers in a nationwide registry of 15,269 HIV/AIDS patients in Taiwan in 1998–2009.¹ Excluded from that cohort were HIV-infected patients under 15 years. In this study we determined the cancer incidence in this group of HIV-infected children and compared their incidence to that of non-infected children in the general population.

With approval from the National Health Research Institutes, Taiwan, the National Health Insurance Research Database (NHIRD) was searched for children younger than 15 years with HIV/AIDS in the 1998–2009 databases as previously described.¹ Patients subsequently diagnosed with cancer were identified based on the ICD-9-CM diagnosis codes. In order to calculate expected rates of cancer, data were obtained from a database linked by the Office of Statistics of the Department of Health using the NHIRD and death certificate database. This dataset consisted of 1.8 million individuals randomly sampled from the Registry for Beneficiaries of the NHIRD, which contains registration and original claim data of every person who was a beneficiary of the National Health Insurance program during the period 1998–2009 (approximately 23.72 million individuals). All individuals under the age of 15, totaling 297,387 individuals, were then selected as the control group.

The incidence density (ID) and standardized incidence rate (SIR) for each cancer type were calculated. Person-years analysis was performed in strata of age, calendar period and cancer type to estimate the ID and SIR. The start date for the calculation of person-years was the

Correspondence and reprint requests to: Yi-Ming A. Chen, M.D., Sc.D., Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan. Tel: +886-2-28267193; Fax: +886-2-28270576; arthur@kmu.edu.tw.

Conflicts of Interest: none to declare

date of first HIV/AIDS clinic visit and the end date was December 31, 2009 as no deaths occurred during the follow-up period. The ID of each type of cancer after HIV infection was calculated by dividing the number of observed cancer cases by the total person years at risk for that cancer. The SIR for each cancer type was calculated by dividing the observed number of cases by the number that would be expected if age-, sex-, and calendar-period-specific rates of the comparison population applied.² The 95% confidence interval (CI) was calculated by Poisson distribution. All analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC). A two tailed *p* value of less than 0.05 was considered statistically significant.

A total of 230 HIV-infected children were identified. There were 131 males and 99 females. Seven of these children were diagnosed with cancer. (Table) When compared with non-HIV-infected children, increased SIRs were seen in HIV-infected children with Kaposi's sarcoma (SIR=30513.7, 95%CI=3426.89–110169.44), cancer of the lung and bronchus (SIR=108.32, 95%CI=1.42–602.67), and cancer of the testis (SIR=106.86, 95%CI=1.4–594.53).

Most of the reported cases of cancer in children with HIV are AIDS-defining cancers such as Kaposi's sarcoma and Non-Hodgkin's lymphoma or non-AIDS defining cancers such as leukemia. Our study showed cancers of the lung and testis, which are very uncommon in children. A case of primary lung cancer in a child with AIDS was previously reported by Biggar et al.³ This study identified the first case of testicular cancer in a child with HIV. Unfortunately, the histopathology of the testicular tumor in this child is unknown.

The only previous study in Asia was performed in Thailand, which reported a 10-times higher incidence of cancers in HIV-infected children compared with non-HIV-infected children, but this study was performed in children born before perinatal antiretroviral therapy.⁴ In the advent of antiretroviral therapy, the incidence of AIDS-defining cancers in children has decreased dramatically⁵, but that of non-AIDS-defining cancers has continued to rise. Epidemiological data suggest that antiretroviral therapy may reduce the incidence of AIDS-defining cancers in children because of improved immunosurveillance induced by antiretroviral therapy.^{6,7} However, immune dysregulation has been reported to persist in some children on antiretroviral therapy.^{8,9} A limitation of this study was that there was no perinatal antiretroviral therapy exposure data, as these data would help confirm whether the cancer incidence was related to antiretroviral exposure. Many of the cancers have been associated with an infectious etiology in HIV-infected adults¹ and children¹⁰. Although a causal role has not yet been established for some cancers, human papilloma virus (HPV) infection has been associated with lung cancer¹¹ and testicular cancer¹² in adults.

Even though this was a nationwide study encompassing 12 years, the number of HIV-infected children in Taiwan is low. This is due to Taiwan Centers for Disease Control's implementation of nationwide antenatal HIV-1 screening and chemoprevention programs in 2005. As a consequence, the number of HIV-infected children with cancer is also low. While regular screening for the whole spectrum of cancers is not recommended in children with HIV due to the small number of cases, the possibility of rare cancers in children under 15 years of age such as lung cancer and testicular cancer has to be kept in mind.

Acknowledgments

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, Taiwan, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes. Funding was provided in part through the Asia Pacific HIV Research Collaboration, an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the U.S. National Institute of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Cancer Institute, as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01AI069907), and from the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

References

1. Chen M, Jen I, Chen YH, et al. Cancer Incidence in a Nationwide HIV/AIDS Patient Cohort in Taiwan in 1998–2009. *J Acquir Immune Defic Syndr*. Apr 1; 2014 65(4):463–472. [PubMed: 24583616]
2. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. *IARC Sci Publ*. 1987; (82):1–406.
3. Biggar RJ, Frisch M, Goedert JJ. Risk of cancer in children with AIDS. AIDS-Cancer Match Registry Study Group. *JAMA*. Jul 12; 2000 284(2):205–209. [PubMed: 10889594]
4. Pancharoen C, Nuchprayoon I, Thisyakorn U, et al. Hospital-based epidemiologic survey of malignancies in children infected with human immunodeficiency virus in Thailand. *Pediatr Infect Dis J*. Oct; 2005 24(10):923–924. [PubMed: 16220094]
5. Chiappini E, Galli L, Tovo PA, et al. Cancer rates after year 2000 significantly decrease in children with perinatal HIV infection: a study by the Italian Register for HIV Infection in Children. *J Clin Oncol*. Jan 1; 2007 25(1):97–101. [PubMed: 17194910]
6. van Leeuwen MT, Vajdic CM, Middleton MG, et al. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. *AIDS*. Oct 23; 2009 23(16):2183–2190. [PubMed: 19734774]
7. Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer*. Jul 27; 2010 103(3):416–422. [PubMed: 20588274]
8. Anselmi A, Vendrame D, Rampon O, Giaquinto C, Zanchetta M, De Rossi A. Immune reconstitution in human immunodeficiency virus type 1-infected children with different virological responses to anti-retroviral therapy. *Clin Exp Immunol*. Dec; 2007 150(3):442–450. [PubMed: 17956580]
9. Gilson RJ, Man SL, Copas A, et al. Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborative HIV Cohort (UK CHIC) Study. *HIV Med*. Feb; 2010 11(2):152–160. [PubMed: 19732175]
10. Chiappini E, Berti E, Ganesin K, et al. Pediatric human immunodeficiency virus infection and cancer in the highly active antiretroviral treatment (HAART) era. *Cancer Lett*. May 28; 2014 347(1):38–45. [PubMed: 24513180]
11. Cheng YW, Chiou HL, Sheu GT, et al. The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. *Cancer Res*. Apr 1; 2001 61(7):2799–2803. [PubMed: 11306446]
12. Garolla A, Pizzol D, Bertoldo A, et al. Testicular cancer and HPV semen infection. *Front Endocrinol (Lausanne)*. 2012; 3:172. [PubMed: 23267350]

Incidence density (ID) and standardized incidence ratio (SIR) of cancers among HIV-infected children in Taiwan between 1998–2009

Table

Cancer	Male			Female			Total		
	ID	SIR	95%CI	ID	SIR	95%CI	ID	SIR	95%CI
Kaposi sarcoma	130.11	Inf*	(Inf,Inf)	177.69	22730.65	(297.09,126470.1)	150.23	30513.7	(3426.89,110169.44)
Non-Hodgkin lymphoma				177.69	61.93	(0.81,344.56)	75.11	2.09	(0.03,11.62)
Liver and biliary system				177.69	1.25	(0.02,6.94)	75.11	0.74	(0.01,4.13)
Bronchus and lung				177.69	606.15	(7.92,3372.54)	75.11	108.32	(1.42,602.67)
Testis	130.11	106.86	(1.4,594.53)						
Leukemia				177.69	0.49	(0.01,2.71)	75.11	0.2	(0.1,1.1)

* SIR for Kaposi sarcoma in males could not be calculated as there were no cases in the general population.