Cancer in adolescents and young adults living with HIV

Julia Bohlius[a], Caroline Foster[b], Gita Naidu[c], Mazvita Sengayi[d,e], Anna Turkova[f,g]

[a]Institute of Social and Preventive Medicine, University of Bern, Switzerland;

[b]900 and Family Clinics, Imperial College NHS Trust, London, UK;

[c]Paediatric Haematology Oncology, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa;

[d]National Cancer Registry, National Health Laboratory Service, South Africa;

[e]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;

[f]MRC CTU, University College London Institute of Clinical Trials and Methodology, London, UK;

[g]Paediatric infectious Diseases Department, Great Ormond Street Hospital, London UK.

Correspondence to:

Dr Anna Turkova, MRCPCH, MSc, MRC CTU, University College London Institute of Clinical Trials and Methodology, 90 High Holborn, London, UK; Tel: +442076704658; e-mail: a.turkova@ucl.ac.uk

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Abstract

Purpose of review: Adults living with HIV have an increased risk of malignancy yet there is little data for adolescents and young adults. We reviewed recently published cancer epidemiology, treatment and outcome data for adolescents and young adults living with HIV (AYALHIV) aged 10 to less than 25 years between 2016 and 2017.

Recent findings: AYALHIV are at increased risk of developing cancer compared to their uninfected peers. Kaposi sarcoma and non-Hodgkin lymphoma occur most frequently with variation by geographical region. Increased cancer risk is associated with HIV-related immunosuppression and co-infection with oncogenic viruses. Published data, particularly on post treatment outcomes remains limited and analyses are hampered by lack of data disaggregation by age and route of HIV transmission.

Summary: Whilst data is sparse, the increased cancer risk for AYALHIV must be modified by improving global access and uptake of antiretroviral therapy, HPV and HBV vaccination, screening for hepatitis B and C infection and optimised cancer screening programs. Education aimed at reducing traditional modifiable cancer risk factors should be embedded within multidisciplinary services for AYALHIV.

Key words: adolescents, young adults, HIV, cancer, prevention

INTRODUCTION

The number of adolescents and young adults living with HIV (AYALHIV) continue to rise due to high rates of new infections and increasing life expectancy on antiretroviral therapy (ART). AYALHIV (between the ages of 10 to <25 years) account for 13% of those living with HIV; the majority of them are from sub Saharan Africa (SSA). Adolescence is the only age group with a rising AIDS-related mortality [1](**Figure 1**).

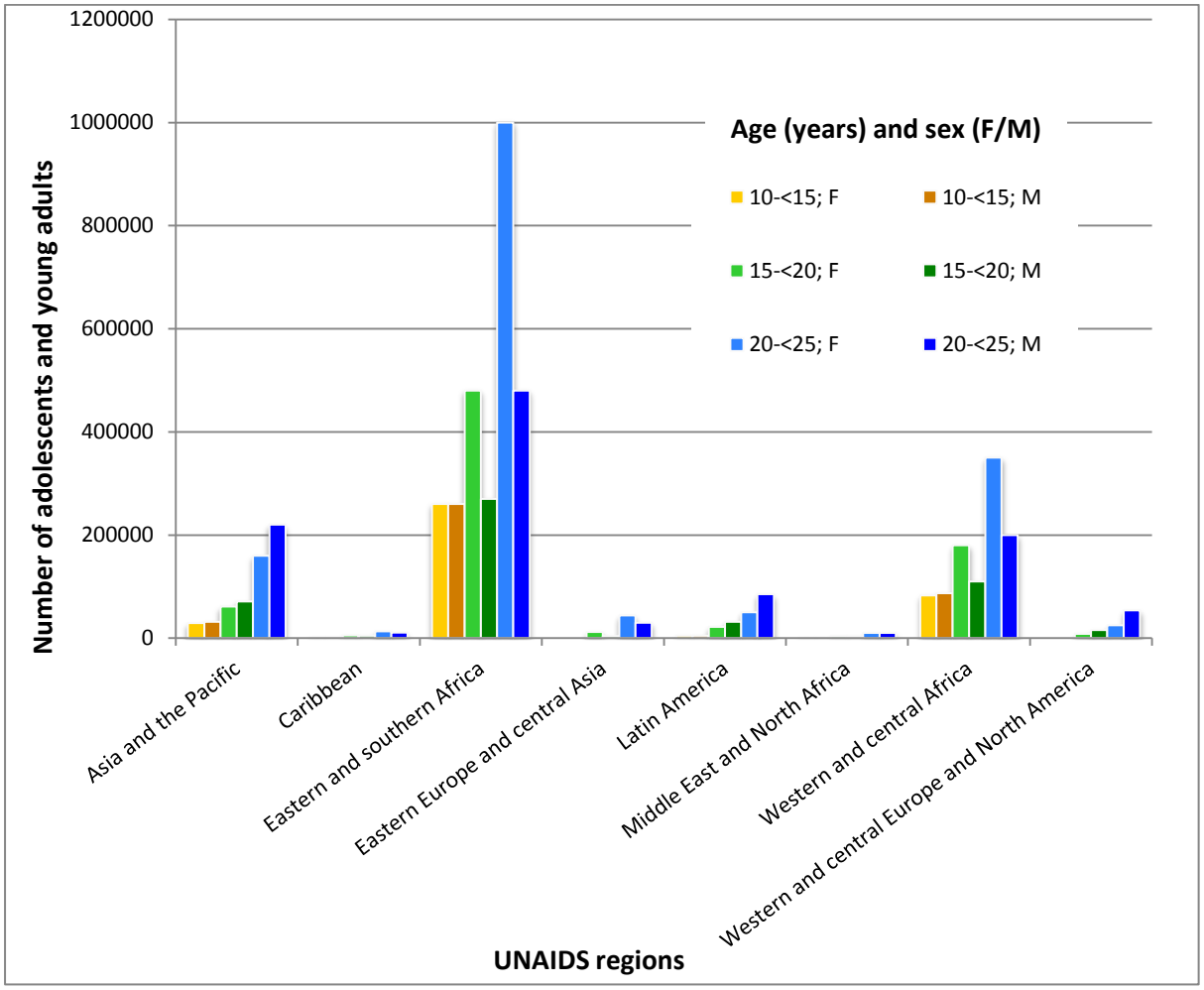

Figure 1. Estimates for number of adolescents and young adults living with HIV in 2016 stratified by age group, sex and UNAIDS region.

Estimates for (i) western, central Europe and North America and (ii) eastern Europe and central Asia for adolescents aged 10 to <15 years are not available. F=female, M=male.

Source: UNAIDS 2017 estimates.

Adolescence, transition and cancer risk

Historically malignancies in people living with HIV are categorized as acquired immunodeficiency syndrome (AIDS)-defining and non-AIDS-defining (Table1) [2,3]. AYALHIV are at increased risk of developing both AIDS and non-AIDS-defining cancers compared to HIV-negative individuals [4]. The increased cancer risk for those living with HIV is driven by interlinked immunosuppression, decreased cancer surveillance, persistent co-infection with oncogenic viruses and HIV viremia. Immediate ART initiation, before immunosuppression occurs, significantly reduces risk of cancer [5,6]. However, AYALHIV have lower rates of ART uptake, increased non-adherence to ART and higher rates of loss to follow up compared to younger children and older adults resulting in poorly controlled HIV [4,7,8].

Table 1. Infection-associated cancers and related clinical HIV stage

Malignancy	Association with oncogenic viruses	HIV Staging*
AIDS-defining malignancies		
Non-Hodgkin lymphoma Burkitt's lymphoma Large cell (immunoblastic) lymphoma Primary central nervous system lymphoma	 EBV EBV	 CDC C WHO 4
Kaposi sarcoma	HHV-8	CDC C, WHO 4
Invasive cervical carcinoma	HPV	CDC C, WHO 4
Non-AIDS-defining malignancies*		
Smooth muscle tumours Leiomyoma (benign) Leiomyosarcoma (malignant)	 EBV EBV	CDC B
Hodgkin lymphoma	EBV	-
Hepatocellular carcinoma	HBV, HCV	-
Anal cancer	HPV	-

*The Centre for Disease Control (CDC) lists NHL, KS and invasive cervical cancer as Category C (AIDS-defining) illnesses and leiomyosarcoma as Category B (symptomatic HIV-infection entities not included in Category C) illnesses [2]. The World Health Organization lists all of these under Clinical Stage 4 and does not classify leiomyosarcoma [3]. **Many other neoplastic disorders, such as anal cancer, oral squamous carcinoma and testicular cancer have been linked to HIV infection and included in the group of non-AIDS-defining illnesses.

Currently, the most frequent cancers in AYALHIV are, depending on geographic region, Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and leiomyosarcoma [4,9–11]. KS is associated with Human Herpes virus 8 (HHV-8) infection; leiomyosarcoma and some NHL subtypes - with Epstein Barr virus (EBV) infection [12,13]. In American adolescents (15-19 years) living with HIV, 49% (95% CI

39-63) of all cancers were attributable to infectious precipitants [9]. Higher rates of unprotected sex in behaviourally infected AYALHIV increase acquisition of sexually transmitted oncogenic viruses including high risk human papilloma viruses (hrHPV) and hepatitis B and C viruses (HBV, HCV) potentiating cervical, oropharyngeal, anogenital cancers and hepatocellular carcinomas (HCC), respectively [13]. Perinatally infected AYALHIV may face increased risk of cancer compared to their behaviourally infected peers due to lifelong exposure to HIV, immune dysregulation and if co-infected perinatally with HBV and/or HCV.

Lastly, the period of transition of health care between paediatric and adult services is associated with poorer health outcomes in many chronic diseases, including HIV [14]. Global models of transition vary widely between countries, income settings and individual diseases and an adolescent living with HIV and a previous or current cancer diagnosis may have to negotiate two independent transition processes [15,16]. For young people living with HIV, transition typically occurs during late teens or early 20s, an age with peak incidence in Hodgkin lymphoma diagnoses within the general population [16–18].

METHODS

We searched PubMed on November 2nd 2017 (search terms are shown in **Box 1**). We restricted the search to January 1st 2016- to November 1st 2017. We identified 289 references, which were reviewed by the authors. We included papers that reported cancer incidence rates, risk factors, survival or prevention interventions in AYALHIV aged 10 to <25 years. Papers reporting incidence rate in adults without further age disaggregation for <25 year olds were not considered. We included original articles, systematic reviews and case reports. Expert reviews were excluded. A few older important studies were used to support key statements.

Box 1: Search strategy for Medline (PubMed)

(("Neoplasms"[Mesh]) OR (neoplasm*[Title/Abstract] OR cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR malignanc*[Title/Abstract] OR leukemi*[Title/Abstract] OR leukaemi*[Title/Abstract] OR hematopoietic stem cell transplantation*[Title/Abstract] OR haematopoietic stem cell transplantation*[Title/Abstract] OR hematopoietic cell transplantation*[Title/Abstract] OR haematopoietic cell transplantation[Title/Abstract])) AND (("Adolescent"[Mesh]) OR ("Young Adult"[Mesh]) OR (adolescen*[Title/Abstract] OR juvenil*[Title/Abstract] OR youth*[Title/Abstract] OR teen*[Title/Abstract] OR under-age*[Title/Abstract] OR underage[Title/Abstract] OR pubescen*[Title/Abstract] OR young adult*[Title/Abstract])) AND (Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human

immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MH])

CANCER EPIDEMIOLOGY IN AYALHIV

In the recent literature there were limited data on cancers disaggregated by age and virtually no data disaggregated by mode of HIV transmission. It was therefore not possible to describe differences in perinatally and horizontally infected AYALHIV. Although paediatric and adult cohorts linking is being developed [19–21], there are only few longitudinal follow up results for cancer risk in children and adolescents transitioning to adult care [22].

Non-Hodgkin lymphoma (NHL)

A single centre cohort study from the UK reported on the increased risk of a new lymphoma diagnoses in young adults living with perinatally acquired HIV (PaHIV) following transition to adult care [22]. Five out of 147 (3.4%) developed lymphoma at a median (range) age of 19 (18-23) years. Patients presented with advanced disease (Ann Arbor stage III/IV), mainly diffuse large B-cell lymphomas, a prolonged history of non-adherence, with a life time average of 14 years with detectable viraemia and a low nadir CD4 count [157 (90-220) cells/µl]. Small numbers precluded formal risk factor analysis, however the NHL incidence rate significantly exceeded that of the age matched general UK population; incidence rate ratio 25.9 (95% CI 8.31 – 61.7), $P < 0.0001$. Treatment outcomes were not reported. This study echoes a previous report from Italy, describing two cases of Burkitt lymphoma in AYALHIV who were chronically exposed to high-levels HIV viremia [23]. These two case series support the concerns of longer term oncogenic risk for the current generation of perinatally infected AYALHIV following prolonged viremia due to late diagnosis, and low rates of viral suppression due to previous inferior ART regimens and suboptimal dosing, non-adherence and the evolution of resistance [22]. Besides improved HIV diagnosis and linkage to care, adherence support and individualised selection of potent and well tolerated ART to achieve virological suppression, as well as greater awareness and prompt investigation of symptoms is needed to diagnose NHL at early stages [22].

Kaposi sarcoma (KS)

We identified one KS case series [24] and two cohort studies reporting incidence rates in AYALHIV [25,26]. A cohort study conducted in Uganda and Kenya reported crude KS incidence rates for AYALHIV (18 to 24 years) higher in ART non users than in ART users [13]. Incidence rates tended to be higher in young men than in women [25] although it is unclear whether this is explained by higher prevalence of HHV-8 [27], delayed access and poorer adherence to ART in young men or additional factors. Another study from Malawi reported a steady increase in KS cases in adolescents per annum despite improved ART coverage [24]. The average annual number of KS diagnoses in children and adolescents from 2006 to 2010 (n = 89) was 17.8 cases per year, compared to 25.2 cases per year from 2011 to 2015 (n = 126) [24]. This may be explained by better KS diagnosis with the improved HIV care [24]. A third study reported KS incidence rates for AYALHIV (aged 16-24 years) from Europe, South Africa, North America and Asia. In this multiregional cohort analysis adolescents in South Africa had very high KS incidence rates (303, 95% CI 176-523) per 100 000 person years, followed by adolescents in Latin America, North America and Europe (**Table 2).**

Table 2: Kaposi sarcoma incidence rate in HIV-positive adolescents and young adults who started antiretroviral therapy

Study	Country / region	Age group [years]	Rate (95% CI) per 100,000 person-years
Semeere 2016 [25]	Uganda, Kenya	18-19	245 (79 – 760)
	Uganda, Kenya	20-24	323 (245 – 426)
Rohner et al 2017 CID [26]	South Africa	16 - 25	303 (176-523)
	Latin America	16 - 25	248 (141-438)
	North America	16 - 25	95 (36-253)
	Europe	16 - 25	115 (93-143)

Invasive cervical cancer (ICC)

Cervical cancer is the fourth leading cause of cancer incidence and mortality for women globally [28,29]. In AYALHIV one cohort study reported an incidence rate for invasive cervical cancer (ICC) in young women (18-25 years) of 223 (100-496) per 100,000 person years [30]. Women living with HIV have higher hrHPV prevalence [31,32] and more diverse HPV subtypes than their HIV negative counterparts [33–35]. HIV-infected young women have high incidence of cervical dysplasia [36];

compared to HIV-uninfected young women the incidence of cervical dysplasia has been reported to be three times higher in HIV-infected young women [37].

Hepatocellular carcinoma (HCC)

HIV/HBV and HIV/HCV co-infections are associated with an increased risk of liver disease including HCC in adults, however there is minimal data in those co-infected either perinatally or in childhood [38]. Two cases of HCC in adolescents are described in the literature. One male, of black African origin, with PaHIV/HBV developed a rapidly progressive HCC aged 19 despite more than a decade of suppressive ART for both HBV and HIV and regular HCC screening. Despite timely surgery he died of recurrent metastatic HCC within a year of diagnosis [38]. A second adolescent with PaHIV developed an HCC but with no evidence of hepatitis co-infection. He had slow disease progression despite being severely immunocompromised, with no evidence of recurrence more than a year from surgical resection [39].

Smooth muscle tumours

A recent study from South Africa reported a case series of EBV-associated smooth muscle tumours in AYALHIV and adults [40]. Five cases occurred in adolescents (10 – 15 years), median CD4 cell count 616 (range 1 – 1331) cells/µL, all were female, and all but one survived [40].

TREATMENT, PROGNOSIS AND SURVIVORSHIP

There were limited published data for cancer outcomes in AYALHIV, however adult studies suggest disparities in access to cancer treatment and poorer outcomes in adults living with HIV compared to their uninfected peers [41]. A retrospective observational study from Malawi reported treatment outcomes for 70 children and adolescents with HIV (median age 8.6 (1.7–17.9) years) diagnosed with KS [42]. Local first-line chemotherapy included bleomycin (B) and vincristine (V). In 2012 doxorubicin became available in Malawi, which was added for second-line therapy. Paclitaxel was used for the third line. ART-naïve individuals started nevirapine-based ART within 2 weeks of chemotherapy. Of all patients, 28% had severe immunosuppression and nearly half were on ART at time of KS diagnosis. The combination of BV plus ART was well tolerated, with minimal severe adverse events. Over half (58%) have survived at median follow-up of 29 (15–50) months. Lymphadenopathic KS, the

most common clinical presentation in children in eastern Africa, was associated with the best outcomes. KS with woody oedema had a more chronic disease course, whereas visceral disease and KS with >20 widespread "disseminated" skin/oral lesions were independently associated with increased mortality. Identifying risk factors associated with unfavourable outcomes may be critical to determining which patients will require alternative therapeutic strategies [42].

Timely ART initiation in individuals with HIV-related malignancies reduces morbidity associated with opportunistic infections and improves overall survival. However, pre-existing HIV-associated organ dysfunction, coexistence of opportunistic infections, compound immunosuppression caused by HIV and chemotherapy, as well as drug interactions between ART and chemotherapy and overlapping treatment-related toxicities make management of patients with HIV and cancer complex. A recent study suggests co-administration of chemotherapy with ART based on integrase strand-transfer inhibitors (INSTI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) but not boosted protease inhibitors results in better safety profiles and higher suppressed viral replication [40].

Adult survivors of childhood/adolescent cancer have a lifelong increased morbidity and mortality as well as amplified risk of secondary malignancy [43]. Morbidity may be multisystem impacting on cardiorespiratory, skeletal, renal, neurocognitive, endocrine and reproductive health compounded with significant psychosocial issues affecting mental health [44]. Annual reviews are recommended for survivors of childhood cancer for screening, prevention and treatment of late effects, however uptake following transition to adult care is poor [45]. AYALHIV who survived malignancy face similar issues compounded by risk of cumulative long term sequelea of HIV. Potentially they have an increased risk of a secondary malignancy due to their underlying immune dysregulation and require enhanced support during transition to ensure retention in care and viral suppression.

PRIMARY AND SECONDARY PREVENTION

Early HIV diagnosis and timely ART may substantially reduce the risk of AIDS-defining cancers [5,6,10,11,46]. Unlike for HPV, HBV and HCV, there are no vaccines or specific treatment for EBV and HHV-8, and early access to suppressive ART remains the most important preventive measure for cancers related to these infections.

High risk variants of Human Papilloma Virus

The high global prevalence of persistent hrHPV infection in both female and male AYALHIV [33,34,47–49] and high proportion of high-grade pre-cancerous lesions [49] highlight the importance of gender-neutral HPV vaccination. HPV vaccination induces good HPV-specific cell-mediated immune responses in AYALHIV, comparable to HIV-uninfected age-matched controls, although 3 rather than 2 doses are still recommended for AYALHIV due to a data gap [50]. Currently only 11 (6%) countries vaccinate males in their national immunisation programmes [51]. World Health Organisation (WHO) and American Society of Clinical Oncology (ASCO) guidance prioritise vaccination of girls based on cost-effectiveness analyses for prevention of cervical cancer; boys can be included if the vaccine uptake among priority female population is <50% and resources are available [51,52]. A relatively high proportion of hrHPV types in young women in SSA, are not covered by currently available HPV vaccines [31,53] which supports early initiation of cervical screening for all sexually active women living with HIV irrespective of age as recommended by WHO and ASCO [51,54]. A study from Saudi Arabia showed that male circumcision may play role in reduction of HPV infection, penile cancers and cervical cancer among women with circumcised partners [55]. Screening for anal cancers is not routinely recommended, although some experts suggest that this might be effective [56,57]. There is an urgent need of prospective studies validating different approaches for prevention and screening of cervical and anogenital cancers.

Hepatitis B and C

Occurrence of HCC early in adulthood underlines the importance of primary prevention with HBV vaccination and screening for chronic HBV and HCV co-infection. Systematic screening for HBV and HCV infection is limited in most sub Saharan African countries [58]. Hepatitis B vaccination from birth with serological monitoring and boosting when appropriate, and education around prevention of HCV acquisition should be embedded within the life span care of those living with HIV. There is no consensus on HCC screening although 6 monthly liver ultrasounds and alpha-fetoprotein are supported by WHO guidance [38,59]. Reducing risk of HCC includes HBV viral suppression with tenofovir-based regimens, avoidance of excessive alcohol and weight optimisation. Increased advocacy for rapid access to curative direct-acting antivirals for HCV for co-infected adolescents is urgently required.

Knowledge, awareness and uptake of sexual and reproductive health services (SRS) is insufficient among young people [60,61]. Enhanced counselling, integration or linkage to SRS can improve the uptake of voluntary male circumcision and cervical cancer screening [62]. AYALHIV require access to

"youth friendly" SRS services integrated within multidisciplinary HIV care that includes primary prevention packages addressing vaccination, ART adherence, smoking [33], alcohol and substance use [63], weight management and where appropriate screening for HPV, HBV and HCV-related malignancies.

CONCLUSION

People living with HIV, including adolescents and young adults are at increased risk of malignancy, due to immune dysregulation and the persistence of oncogenic viruses. Whilst the excess cancer risk is reduced with suppressive ART, ART coverage is still suboptimal in many settings, and AYALHIV have the lowest rates of engagement with each aspect of the HIV care cascade. Improving HIV diagnosis, linkage and retention in care on sustained suppressive ART for AYALHIV remains the most important cancer preventative measure. However, this must go hand in hand with integrated cancer screening and education programs including prevention of traditional cancer modifiable risk factors for a vulnerable population who currently face an increased life time risk of malignancy, whilst they negotiate their transition to adulthood living with HIV. Increased awareness among health care workers and prompt investigation of suggestive symptoms is needed to diagnose cancers at early stages. In the era of effective ART, AYALHIV should have access to cancer treatment and supportive care comparable to their uninfected peers.

KEY POINTS

- AYALHIV are at increased risk of AIDS and non-AIDS defining malignancies, associated with immune dysregulation and co-infection with oncogenic viruses.
- Non-Hodgkin lymphoma and Kaposi sarcoma are the commonest malignancies occurring in AYALHIV globally.
- Reducing the risk of cancer in AYALHIV requires increased access to suppressive ART, HPV and HBV vaccination, screening and treatment for HBV/HCV coinfection and programmatic screening for cervical and anogenital cancers.
- Improvement in cancer estimates for AYALHIV requires data disaggregated by age and route of HIV transmission which is currently lacking.
- Enabling long-term follow-up of children and adolescents living with HIV, including survivors of a dual diagnosis of HIV and malignancy as they transition into adult services, requires effective linkage of paediatric and adult cohorts.

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Conflicts of interest

No conflicts of interests were declared.

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