Original Article

Spectrum of malignancies among human immunodeficiency virus-infected patients at a tertiary level human immunodeficiency virus-anti-retroviral therapy center in a North Indian hospital

Sumit Arora, Ashwin Mahesh, Nalin Kumar Mahesh, Niket Verma
Department of General Medicine, Army College of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Niket Verma, Department of General Medicine, Army College of Medical Sciences, Delhi Cantt, New Delhi - 110 010, India.
E-mail: drniketverma@gmail.com

Abstract

Introduction: Human immunodeficiency virus (HIV)-infected individuals have a higher risk of some types of cancer. A chronic immunodeficiency state, increased survival in the highly active antiretroviral therapy (HAART) era and predisposition to certain oncogenic viral infections have been postulated as the main reasons. While, the incidence of acquired immunodeficiency syndrome (AIDS) defining cancers (ADCs) is declining in the post-HAART era, non-AIDS-defining cancers (NADCs) are becoming an important cause of mortality in these patients. **Materials and Methods:** Analysis of the data of HIV-infected patients registered at an apex centre was done for 7 years. All patients were subjected to routine investigations on presentation (baseline) and during follow-up for the occurrence of any malignant disease. CD4 cell counts before starting anti-retroviral therapy and before the diagnosis of malignancy were noted. The date of the last review and the current status/outcome were recorded. **Results:** Out of 1258, 17 patients were diagnosed with various malignancies. Seven patients (41.2%) had ADCs and the remaining 10 (58.8%) had NADCs. The mean duration between diagnosis of HIV infection and diagnosis of malignancy was 59.53 months. The mean survival duration from the diagnosis of malignancy for all cases was 21 months. The mean survival duration was 29 months and 15 months for ADC and NADC group respectively. **Conclusions:** NADCs are on the rise in the era of effective use of HAART and increasing life span of HIV patients. The index of suspicion for cancer should be higher in such patients, especially compared to opportunistic infections in view of good immunovirologic status.

Key words: Carcinoma, CD4 lymphocyte count, human immunodeficiency virus infections, squamous cell, viral load

INTRODUCTION

In 2015, the prevalence of human immunodeficiency virus (HIV) infection in the adult population (15–49 years) was estimated to be 0.22% (0.16–0.30) in India and the population of persons living with HIV (PLHIV) was estimated to be approximately 21.40 lakhs.[1] Approximately eighty-seven thousand people were newly infected with HIV in 2015, while 69.11 thousand PLHIV died from acquired immunodeficiency syndrome (AIDS)-related causes in the same year in India.[1,2]

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People infected with HIV have a substantially higher risk of some types of cancer compared with uninfected people of the same age.[3] A chronic immunodeficiency state and predisposition to certain oncogenic viral infections has been postulated as the main reason.[4] Some have attributed this to the increased survival of HIV-positive individuals in the highly active antiretroviral therapy (HAART) era. It has also been postulated that AIDS is a state of chronic inflammation, which may be responsible for oncogenesis. The general term for these cancers is "HIV-associated cancers." Three of these cancers are known as "AIDS-defining cancers/AIDS-defining malignancies" (ADCs/ADMs): Kaposi sarcoma, aggressive B-cell non-Hodgkin lymphoma (NHL), and cervical cancer. It has been reported in various studies that the incidence of ADCs is steadily declining in the post-HAART era.[5] However, the incidence of non-AIDS-defining cancers (NADCs)/ non-AIDS-defining cancer malignancies has been reported to be steadily rising due to prolonged survival of HIV patients and they now figure as an important cause of mortality in these patients.[5-7]

Most of the data regarding ADCs and NADCs comes from the developed world. There have been few recent Indian studies elaborating their epidemiology mostly from regional centres. Two recent studies which studied the spectrum of malignancies in HIV-infected individuals focused either on North Indian[8] or South Indian[9] patients. We conducted an ambispective study conducted at an armed forces centre catering to patients hailing from all parts of the country providing more diverse data. This data can be helpful in planning targeted prevention and intervention efforts aimed at HIV positive individuals for the prevention and treatment of such malignancies. The aim of the current study was to analyze the prevalence pattern and changing trends of malignancies in HIV-positive individuals and to correlate the prevalence pattern of malignancies in HIV-positive individuals with CD4 cell counts and HIV viral loads.

MATERIALS AND METHODS

The present study was an Ambispective Study, conducted at an Apex Immunodeficiency Centre of a tertiary care hospital based in New Delhi. The hospital is a referral centre for HIV patients who are either serving in or have retired from the Indian Armed Forces (and their dependants). The center provides free of cost HAART for HIV-positive patients in accordance with the WHO and National AIDS Control Organization guidelines. A retrospective and prospective analysis of the data of HIV-infected patients registered in the centre was done for 7 years from January 2011 to January 2018. The authors have included the data of only those patients who were on their first visit to the centre.

Inclusion criteria

All HIV-infected patients >18 years of age with/ without confirmed malignancy.

Exclusion criteria

All HIV-infected patients <18 years of age.

All new patients were subjected to routine investigations on presentation (baseline) and during routine follow-up visits for the occurrence of any malignant disease. Various parameters were noted, included demographic details, date of detection of HIV infection, date of starting anti-retroviral therapy (ART), drugs given in the ART regime, date of diagnosis of malignancy, type of malignancy and period from starting ART to the diagnosis of malignancy. The clinical profile included testing for HIV RNA (copies/ml), complete blood counts, biochemical profile and chest X-Ray, Ultrasonography (USG) abdomen. Hepatitis B surface antigen, anti-hepatitis C virus (HCV) and Venereal Disease Research Laboratory were done to check for the presence of co-infection with hepatitis B, hepatitis C and syphilis. The last CD4 cell counts before starting ART and before the diagnosis of malignancy were noted. In case of change in the ART regime, the reason for change and the drugs given in the new regime was also noted. Finally, the date of the last review and the current status/outcome were recorded. The study was approved by the ethical committee of the institute. For retrospective analysis, patient records were used and a history of the development of malignancy was noted. Values of the appropriate tests were noted.

Statistical analysis was conducted using the latest version of SPSS Software (IBM). Mean values were compared using Student's "*t*" test unpaired. Proportions were compared using the Chi-square test. Kaplan–Meier survival graphs were constructed to depict survival among cases with ADCs and NADCs.

RESULTS

During the study period, the record of 1258 patients was reviewed. A total of 17 patients were diagnosed with various malignancies. Out of the 17, seven (41.2%) were female and ten (58.8%) were male. Seven patients (41.2%) had ADCs and the remaining 10 (58.8%) had NADCs. The mean age of patients at the time of the diagnosis of malignancy

was 45.82 years. The mean age for male and female patients at the time of diagnosis of malignancy was 46.60 and 44.71 years, respectively. The malignancies diagnosed in these 17 patients included NHL in four patients, squamous cell carcinoma cervix in three patients, Hodgkin's lymphoma in two patients, squamous cell carcinoma anal canal in two patients and carcinoma lung, carcinoma breast, acute myeloid leukemia, chronic myeloid leukemia (CML), squamous cell carcinoma tongue, and carcinoma larynx in one patient each [Figure 1].

The mean duration between diagnosis of HIV infection and initiation of ART was 12.14 months. The mean duration between diagnosis of HIV infection and diagnosis of malignancy was 59.53 months and the mean duration between initiation of ART and diagnosis of malignancy was 12.14 months. In one patient, these two values are negative because the malignancy was diagnosed first and the HIV infection was diagnosed later.

The mean hemoglobin, total lymphocyte count, platelet count values and other parameters among patients with NADCs and ADCs are given in Table 1. None of the patients in our study tested positive for syphilis, hepatitis C or hepatitis B. The mean HIV RNA value (copies/ml) was 252464.24. The individual values showed a wide variation and ranged from 0 to 2,710,720. The mean values in NADC and ADC patients were 95821.70 and 476239.29, respectively 0.08 out of 17 patients were virologically well suppressed (i.e. viral load <400) on successful ART of which 2 had ADCs (both cervical cancer) and 6 (acute myeloid leukemia-01, CML-01, anal canal-01, larynx-01, breast-01,

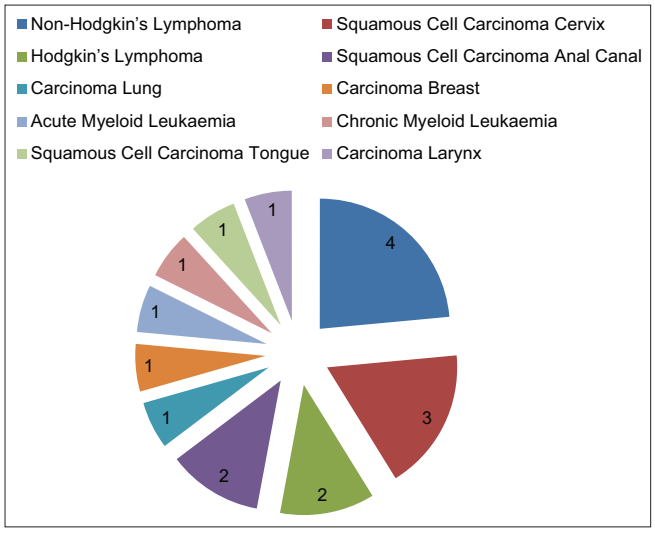

Figure 1: Frequency distribution of various malignancies in human immunodeficiency virus positive patients

Hodgkins-01) had NADCs. Of the nine patients who had high viral loads five had ADCs and four had NADCs.

Mean CD4+ cell count before ART initiation were 167.88 (median: 136.00; range 49–484) cells/µl and at the time of diagnosis of malignancy were 343.69 (median: 253.50; range 10–801). The mean CD4+ cell count at the time of diagnosis of ADC was 248.33 and at the time of diagnosis of NADC was 400.9 cells/µl. Although the mean CD4+ cell count of individuals with ADC is lower than those with NADC it is not statistically significant. Mean CD4+ cell count values for patients with ADC and NADC are given in Table 2.

Of the 17 patients diagnosed with malignancy, 10 were alive at the time of the last review (between October 2017 and June 2018). The mean survival duration from diagnosis of malignancy for all cases was 21 months. The mean survival duration was 29 months and 15 months for ADC and NADC group, respectively. These data are presented in Figures 2-4 as Kaplan–Meier curves.

The treatment regime given to the 17 patients diagnosed with malignancy is given in Table 3. 12 out of the 17 patients had good adherence to treatment (>95%). Three patients were poorly compliant to therapy. Two patients started ART at the time of diagnosis of malignancy hence prior compliance is not required.

DISCUSSION

In this study, we analyzed the incidence of ADCs and NADCs in HIV patients at our center and correlated the incidence and type of malignancies with the CD4 cell counts and viral loads. The incidence of malignancies in our cohort of HIV patients was 1.35%. Two other studies from north India by Sharma *et al*.[10] and Sachdeva *et al*.[8] have revealed an incidence of 1% each in their studies. The plausible explanation for the low rates may be the overall low background rate of malignancies in the Indian population compared to the Western population,[11] and the lack of screening programs for cancer in these patients.[10]

The incidence of NADCs was more than ADCs which suggests changing epidemiology of cancers associated with HIV. Though most Indian studies in the past have shown a higher or equal preponderance of ADCs compared to NADCs[8,10] a recent trend towards increasing incidence of NADCs and declining incidence of ADCs has been seen. Data from the Western

Table 1: Mean laboratory parameter values for all 17 cases diagnosed with malignancies and separately for patients with nonacquired immunodeficiency syndrome defining cancers and acquired immunodeficiency syndrome-defining cancers respectively

Parameter	Mean values			*P*
	Among all 17 cases	Among NADC patients	Among ADC patients	
Hb	11.30	11.35	11.23	0.875
TLC	6981.96	7846.13	5747.43	0.311
Neutrophil	63.88	64.40	63.14	0.840
Lymphocyte	26.47	25.60	27.71	0.695
Platelet count	294588.24	341600.00	227428.57	0.285
Urea	22.89	23.38	22.19	0.776
Creatinine	0.85	0.83	0.86	0.872
SGOT	28.81	27.31	30.96	0.528
SGPT	38.62	43.51	31.61	0.432

NADCs=Nonacquired immunodeficiency syndrome defining cancers; ADCs=Acquired immunodeficiency syndrome-defining cancers; Hb=Hemoglobin; TC=Total leucocyte count; SGOT=Serum glutamic oxaloacetic transaminase; SGPT=Serum glutamic pyruvic transaminase

Table 2: Mean CD4+cell count values for patients with nonacquired immunodeficiency syndrome defining cancers and acquired immunodeficiency syndrome-defining cancers

Parameter	Mean values		*P*
	Among NADC patients	Among ADC patients	
CD4+cell counts prior to ART initiation	208.00	110.57	0.102
CD4+cell counts at the time of diagnosis of malignancy	400.90	248.33	0.268

NADCs=Nonacquired immunodeficiency syndrome defining cancers; ADCs=Acquired immunodeficiency syndrome-defining cancers; ART=Anti-retroviral therapy

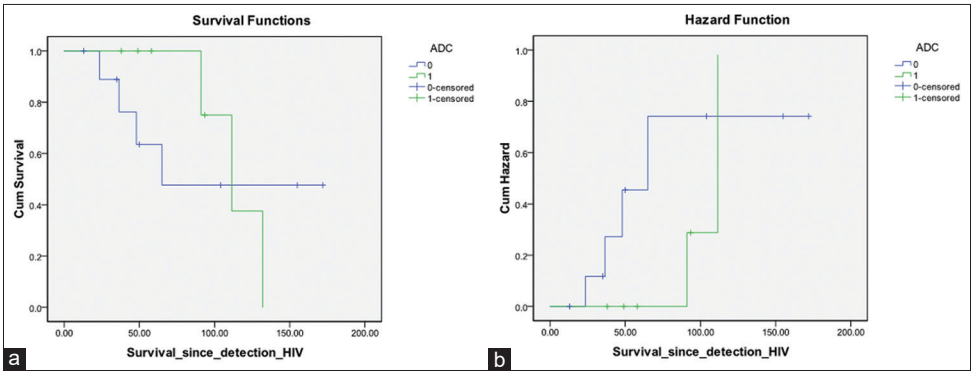

Figure 2: (a and b) Kaplan–Meier curves for survival since detection of human immunodeficiency virus

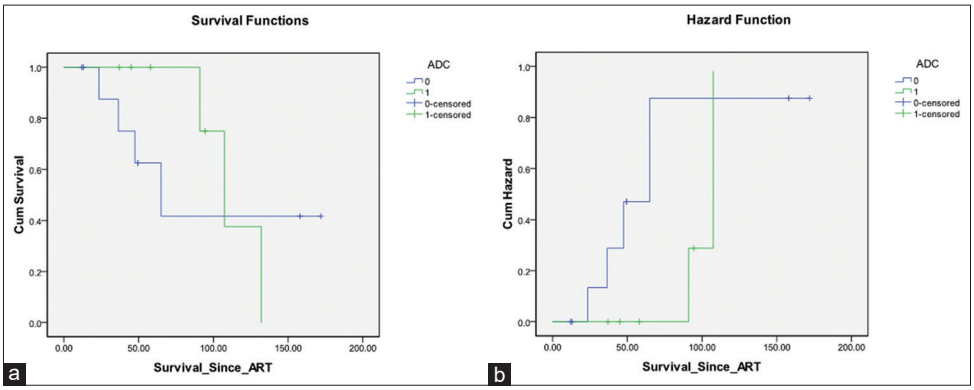

Figure 3: (a and b) Kaplan–Meier curves for survival since institution of anti-retroviral therapy

countries show higher rates of ADC in the pre-HAART era which has declined in the HAART era; whereas, rates of NADCs have risen over the period.[12-16]

In spite of the overall decline in incidence, NHL had the highest incidence (23.5%) followed by carcinoma cervix (17.6%) which is similar to most other studies

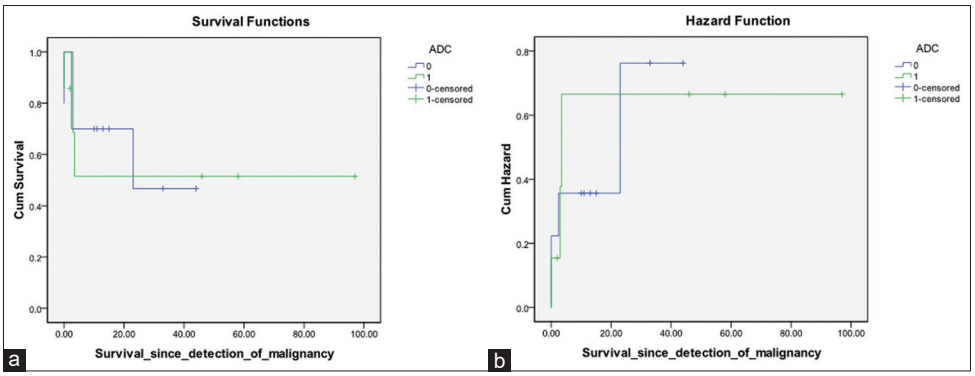

Figure 4: (a and b) Kaplan–Meier curves for survival since date of detection of malignancy

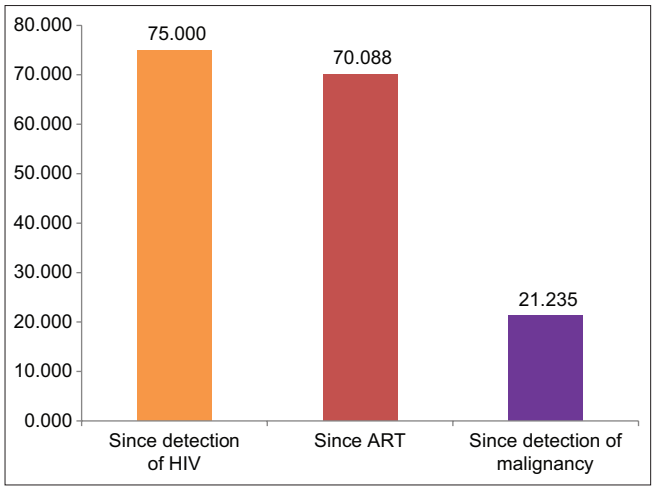

Figure 5: Mean overall survival times (in months) since detection of human immunodeficiency virus, institution of anti-retroviral therapy and detection of malignancy respectively

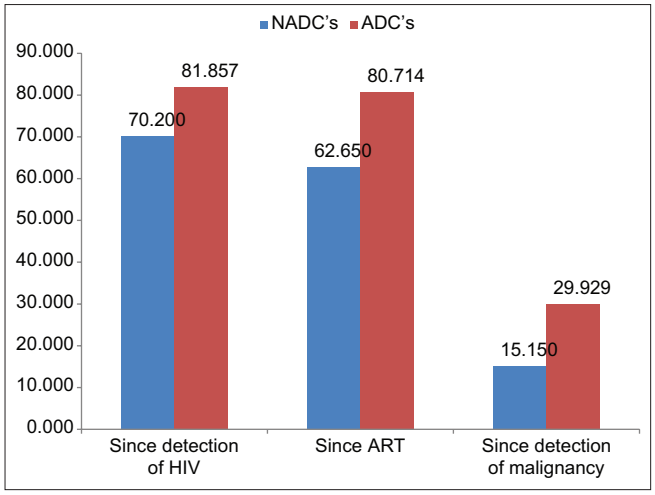

Figure 6: Mean survival times in patients with nonacquired immunodeficiency syndrome defining cancer's and acquired immunodeficiency syndrome defining cancer's (in months) since detection of human immunodeficiency virus, institution of anti-retroviral therapy and detection of malignancy respectively

from India as well as western countries.[8,9,15,16] Among NADCs carcinoma anal canal and Hodgkin's lymphoma (11.76% each) were the most common.

Table 3: Anti-retroviral therapy regime given to the 17 patients

Patient serial number	Malignancy	Treatment regime
1	Carcinoma cervix	SLN, ZLN, TLN
2	Primary pulmonary lymphoma	ZLN-TLL/r
3	Carcinoma lung with brain metastasis	TLN
4	Acute myeloblastic leukemia	ZLA/r
5	Hodgkin's lymphoma	TLE
6	Non-Hodgkin's lymphoma	ZLN
7	Carcinoma cervix	TLE
8	Carcinoma anal canal	ZLN-TLL/r
9	Hodgkin's lymphoma	TLE
10	Non-Hodgkin's lymphoma	TLE
11	Carcinoma breast	TEE
12	Carcinoma cervix	TLE
13	Carcinoma anal canal	TLE
14	Squamous carcinoma tongue	TLR
15	Chronic myeloid leukemia	ZLE
16	Carcinoma larynx	TLE
17	Non-Hodgkin's lymphoma	ZLN

ZLN=Zidovudine, lamivudine, nevirapine; ZLE=Zidovudine, lamivudine, efavirenz; TLE=Tenofovir, lamivudine, efavirenz; SLN=Stavudine, lamivudine, nevirapine; TLL/r=Tenofovir, lamivudine, lopinavir/ritonavir; ZLA/r=Zidovudine, lamivudine, atazanavir/ritonavir

There were no cases of Kaposi's sarcoma. Kaposi's sarcoma which is a common ADC in the Western population and constitutes a significant proportion of the malignancies is rarely seen in India.[17] None of the Indian studies (other than case reports) we referred to reported cases of Kaposi's sarcoma.[9,18,19]

Common NADCs seen in other Indian studies had a similar pattern of incidence with Hodgkin's lymphoma, carcinoma anal canal, and head-neck cancers being the most common.[5,8,10,20]

Oncogenic viruses play an important etiologic role in many ADCs and NADCs. Epstein-Barr virus (EBV) is implicated for most of the HIV associated lymphomas.[21] One-third of head and neck cancers, including most oropharyngeal cancers, and cervical

and anal cancers in patients with HIV-AIDS are related to human papillomavirus infection. We had 12 out of 17 patients in whom oncoviruses may be etiologically associated with cancer highlighting the immense importance of preventable vaccination in some of these patients. Four cases of NHL and two Hodgkin's disease (EBV associated), three cervical, two anal canal and possibly one case of carcinoma larynx (young patient with no history of smoking) may be attributed to HPV infection. There was no case of HBV or HCV associated cancer in our study.

Although the role of baseline CD4+ cell count (i.e., CD4+ count before the initiation of antiretrovirals) in the diagnosis of malignancy is controversial.[22,23] It is seen that the risk of NHL increases with decreasing CD4 cell counts.[24] However, the risk of cervical cancer remains high even in patients with relatively improving CD4 counts.[24] In our study, the mean CD4 at the time of diagnosis of malignancies was found to be much lower in ADCs, especially NHLs compared to NADCs suggesting a greater role of immunosuppression in ADCs and prolonged life span and chronic inflammatory state associated with long-term HIV infection in NADCs. Cervical cancer, as suggested by Biggar *et al*.[24] was seen in both high and low CD4 groups.

We corroborated the incidence of malignancies with HIV viral loads at the time of diagnosis and found that majority of the patients presenting with malignancy with well-suppressed viral loads had NADCs and the rest had cervical cancer. All cases of NHL had high viral loads at the time of diagnosis suggesting advanced HIV disease and immunosuppression was a major risk for NHLs. NADCs presented more often in patients on stable ART with well-suppressed viremia. Cervical cancer was seen to occur in both subsets.

A diagnosis of malignancy in an HIV patient adds to significant mortality and morbidity. As per Achenbach *et al*.[6] patients with higher CD4+ cell counts at cancer diagnosis, who achieved HIV-RNA suppression (≤400 copies/ml) on HAART, received any cancer treatment, and had ADC or infection-related NADCs compared to infection-unrelated NADCs had better outcomes.

Fifty-eight percent of our patients succumbed to cancer. Mortality rates were similar in both ADCs and NADCs, but the mean duration of survival was much lower (though not statistically significant) in the NADC group even though the majority of them were on successful HAART [Figures 5 and 6].

When we studied individual cases we found that in patients with better immunovirologic and clinical status, the index of clinical suspicion for a severe illness was low leading to a delay in diagnosis of cancer. On the other hand, patients with poor clinical and immunovirologic status are on better follow-up and evaluated more aggressively probably leading to early diagnosis and management of cancer and also ART failure. There was no difference in outcomes in infection-related and infection-unrelated NADCs.

CONCLUSIONS

The incidence of NADCs is on the rise in the era of effective and widespread use of HAART and the increasing life span of HIV patients. The index of suspicion for cancer should be higher in such patients, especially compared to opportunistic infections in view of good immunovirologic status. Finally, the role of increasing the use of HPV vaccine in HIV patients needs to be studied further as this holds a possibility of significantly bringing down the incidence of emerging NADCs in this population.

Limitations

The number of participants in the study is not sufficient to generalize the findings to the entire population of India. A similar study with more number of participants and involving more number of HIV centers across the country is needed.

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Conflicts of interest

There are no conflicts of interest.

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