Journal of Carcinogenesis

Review Article

Intersection of Smoking, Human immunodeficiency virus/acquired immunodeficiency syndrome and Cancer: Proceedings of the 8th Annual Texas Conference on Health Disparities

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Published: 05 October, 2013
Journal of Carcinogenesis 2013,12:18
This article is available from: http://www.carcinogenesis.com/content/12/1/18

Received: 09 July, 2013
Accepted: 20 July, 2013

Abstract

The Texas Center for Health Disparities, a National Institute on Minority Health and Health Disparities Center of Excellence, presents an annual conference to discuss prevention, awareness education and ongoing research about health disparities both in Texas and among the national population. The 2013 Texas Conference on Health Disparities brought together experts, in research, patient care and community outreach, on the "Intersection of Smoking, Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and Cancer". Smoking, HIV/AIDS and cancer are three individual areas of public health concern, each with its own set of disparities and risk factors based on race, ethnicity, gender, geography and socio-economic status. Disparities among patient populations, in which these issues are found to be comorbid, provide valuable information on goals for patient care. The conference consisted of three sessions addressing "Comorbidities and Treatment", "Public Health Perspectives", and "Best Practices". This article summarizes the basic science, clinical correlates and public health data presented by the speakers.

Keywords: Cancer, health disparities, human immunodeficiency virus/acquired immunodeficiency syndrome, smoking

INTRODUCTION

Identifying challenges and barriers to healthcare in underserved communities is the first step in eliminating disparities and providing tailored healthcare. Clinicians, public health professionals and educators/researchers have very important roles to play in eliminating health disparities. The University of North Texas Health Science Center has been actively involved in combating the problem of health disparities in Texas by promoting research, education and training activities for underrepresented minorities, through the Texas Center for Health Disparities. As part of its education and outreach activities, the center organized its 8th Annual Conference on Health Disparities on May 30 and 31, 2013. The overall theme for the conference was "Intersection of Smoking, Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome and Cancer". Chaired by Dr. Jamboor K. Vishwanatha and co-chaired

Access this article online

Quick Response Code:

Website: www.carcinogenesis.com

DOI: 10.4103/1477-3163.119388

by Dr. Johnny He, Dr. Vicki Nejtek and Dr. Jackie Meeks, the conference had over 400 attendees including experts in research, clinical and community practices (public health professionals, policy leaders, educators) in the fields of HIV/AIDS, smoking and cancer as well as highly enthusiastic graduate and undergraduate students. The conference kicked off with an inspirational performance by the local Samaritan House Choir.

Tobacco smoking, HIV/AIDS and cancer are all known to disproportionally affect various minority populations. According to 2011 Centers for Disease Control and Prevention (CDC) statistics, the highest percentage of smokers in the US are the non-Hispanic American Indian (AI)/Alaska native population, closely followed by the non-Hispanic multiple race. As of 2012, 17.9% of the Texas population comprise of smokers. Various risk factors, including tobacco and alcohol consumption, are attributed to HIV/AIDS and cancers. Multiple parameters, including the social and economic status (SES) of the individual, play critical roles on the disease continuum (from prevention and screening to the end of life). Though the highest rates of HIV infection are in the coastal states, Texas is not far behind.[1,2] The overall highest new infection rates are among non-Hispanic blacks and men who have sex with men (MSM).[2-4] There is accumulating evidence that smoking is highly prevalent among persons living with HIV/AIDS (PLWHA) and this is associated with low SES and stigma resulting in illicit substance and alcohol abuse and mental illness; thus, forming a vicious cycle with lesser means to prevent the disease continuum from ending the lives of individuals.[5] The third area of concentration in this conference, cancer, also has very disparate incidence and death rates among the various racial and ethnic populations[6] and the type of cancer (Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion). Though black men and white women have the highest rates of overall cancer incidence, mortality is highest among blacks. Interestingly, lung cancer is one of the leading causes of cancer-related deaths and this is also very closely associated with smoking and tobacco use (CDC, National Cancer Institute, American Cancer Society). The intricate attempts to determine the cause and effect relationships between smoking, HIV/AIDS and cancer and find an intervention/cure are underway at both the scientific and community levels.

From an educational perspective, presentations and discussions by renowned clinicians, researchers, community workers and other public health professionals closely investigated the interplay between the three mentioned health disparities in the 8th Annual Texas Conference on Health Disparities. The first keynote address by Dr. Jack E. Burkhalter formed a strong framework on which the entire conference continued. He provided various statistics on the incidence and comorbidity rates, categorically. His initiatives and involvement in the Tobacco Cessation Program (AIR) and motivational interviewing showed his commitment to "making the difference (he) wished to see,"[7] a concept re-iterated and re-emphasized at multiple junctures in the conference. Following this was the educational first session by Dr. Ellen R. Gritz, Dr. Roger Bedimo and Dr. Erica I. Lubetkin, focusing on "Comorbidities and Treatments". The next day began with a key note address by Dr. Raymond Niaura concentrating on PLWHA. The relationship between smoking and HIV/AIDS was brought to light in his presentation and elaborate evidence showed that smoking cessation indeed resulted in tangible health improvements including longevity. He also emphasized the importance of pharmacological interventions along with motivational intervention and drew attention to response prediction disparities between various ethnic groups.[8] AURORA, an initiative led by him with other co-investigators, is a culturally targeted smoking cessation intervention for Latinos with HIV. This "Public Health Perspectives" session was furthered by interesting and thought provoking presentations by Dr. Walter Royal, III, Dr. Yessenia Castro and Dr. Subhash C. Chauhan. The final session of the conference on "Best Practices" highlighted interventions and the next steps. Dr. Scott T. Walters, Dr. Damon J. Vidrine and Dr. Raymond Niaura presented various algorithms designed and the studies they conduct to determine positive and negative outcomes. Each session concluded with an exciting and highly interactive panel discussion throwing light on the concerns that health professionals face while dealing with the clinical and scientific puzzles.

COMORBIDITIES AND TREATMENTS

The first session commenced with the keynote address by Jack Burkhalter, PhD, on "The Intersection of Smoking, HIV/AIDS and Cancer". Dr. Burkhalter[5,7,9] introduced the subject of the conference by discussing how frequently smoking, HIV/AIDS and cancer are found to be comorbid in patients. There are many racial and geographic disparities with smoking, HIV and cancer. Hispanics tend to smoke less than African Americans and white non-Hispanics, which is a rare positive disparity. It helps explain why New York and Texas have the same prevalence of smokers even though New York has a full smoking ban and high cigarette prices; all because Texas has a higher percentage of Hispanic population. Coastal states have a higher prevalence of HIV while African Americans and MSM have higher percentages of new incidence HIV. In addition, there is a geographic disparity between cancer incidence and cancer-related death

rates in the US. Due to the longer survival rates of PLWHA, cancer incidence has risen within the population. The prevalence of tobacco use and cancer is higher in PLWHA, explained through confounding factors such as low SES, leading to depression that could result in smoking. There are many carcinogens and toxic agents in cigarette smoke that make it a leading cause of death in the US. Nicotine is the addictive agent while tobacco interrupts innate and adaptive immunity, an important problem for PLWHA who are already immunosuppressed. Tobacco dependence is a result of both physical dependence on nicotine and psychological dependence. There have been many tobacco cessation trials in HIV/AIDS patients. Dr. Burkhalter's recent study titled "Aspirations, Inspiration, Respiration: Feasibility of Tobacco Use Intervention with Low-Income PLWHA in Community-Based AIDS Service Organizations" (AIR) found that PLWHA are more motivated to quit smoking when given personalized respiratory feedback, a supportive care environment, autonomy and competency support and when their aspirations and goals are elicited. The study's first phase was completed with a small sample size, but provided promising data about support and feedback that can improve quit rates.

Providing a different perspective on the relationship between smoking and cancer was Ellen Gritz, PhD, in her presentation, "Smoking Cessation in the Oncology Setting-How Smoking Adversely Affects Cancer Treatments and Outcomes". The projected incidence of cancer is driven disproportionately by age and race, with Hispanics showing a much faster rate of growth compared to African Americans followed by Caucasians.[10] There has been a decline in cancer mortality due to decreased rates of smoking, with tobacco being the primary contributor to cancer risk, early detection and other medical advances. A large number of cancer survivors who smoke are between the ages of 18 and 44 (CDC). This statistic is important as smoking interferes in radiation, surgical and chemotherapies for cancer patients. A study was conducted at MD Anderson on self-reported smoking status of the head and neck cancer patients. Discrepancies were found between the self-reported tobacco use and blood cotinine tests, although the discrepancies improved with weekly testing versus baseline tests. Another interesting finding was that patients with cancers that were less strongly associated with smoking have lower long-term quit rates. Notably, Dr. Gritz pointed out that smoking cessation interventions need to be tailored to each individual cancer patient as a head/neck cancer patient might be unable to substitute smoking with food replacements as would be recommended to another patient.[11] In addition, it was found that many cancer centers lack the resources necessary to help with smoking cessation, whereas they were equipped for nutritional counseling. In order to address some of the aforementioned issues, MD Anderson developed a Tobacco Treatment Program that involved behavioral counseling, prescription medications and nicotine replacement, a multidisciplinary team, and assessments and treatment of comorbid psychiatric disorders at no charge. There is a need for more and better tobacco cessation interventions and trials within the cancer patient population as many National Cancer Institute trials performed have not assessed tobacco use and those that did have not assessed use history.[12]

Moving on to clinical perspectives, Roger Bedimo, MD, MS, FACP, presented the topic of "Non-AIDS Complications: Malignancies among HIV-infected Patients". Due to the introduction of highly active anti-retroviral therapy (HAART), there has been increased survival and aging in HIV-infected patients, which has led to a higher incidence of non-AIDS-defining cancers among that population. Lung cancer, anal carcinoma, Hodgkin lymphoma, melanoma and colorectal cancer-all have increased incidence in HIV positive individuals. Studies have found that the risk of non-AIDS defining malignancies (non-ADM) among HIV-infected patients is much higher than that of the HIV-uninfected population, even after adjusting for age, gender and race.[13] Although many complications of AIDS are related to low CD4 counts, many of the non-ADM have not been found to be associated with low CD4 counts. Interestingly, studies have shown that the spectrum of non-ADM among HIV-infected individuals is similar to that of solid-organ transplant recipients, implying the effect on cancer immune surveillance. PLWHA have a higher prevalence of cardiovascular disease risk factors - smoking, elevated triglycerides and lower levels of high density lipoprotein cholesterol.[14,15] In one study, HIV positive veterans had an increased risk of incident acute myocardial infarctions compared to uninfected veterans,[16,17] although the metabolic complications are related to the risk factors with cardiovascular disease. The increased risk of non-ADM is not entirely accounted for by higher prevalence of traditional malignancy risk factors among HIV-infected patients, such as differences in lifestyle, smoking, oncogenic potential of viral co-infections, HAART and immune deficiency. Though, the clinical prognosis of non-ADM may differ between HIV-infected and uninfected patients, there is some evidence that non-ADM show improved prognosis, suggesting a health disparity in the HAART era, for treating malignancies. Furthermore, there is no solid evidence for HIV-specific cancer prevention guidelines for the non-ADM.

Concluding the first session, Erica I. Lubetkin, MD, MPH, discussed "Assessing Cancer Programming Needs and Resources of AIDS Service Organizations and their Clients: Using Qualitative Findings to Develop a Quantitative

Survey". Nearly 25% of all AIDS patient deaths are due to non-HIV-related causes such as smoking, poverty and racial health disparities. The combination of normal aging, lifestyle risk factors, drug toxicities, persistent immune dysfunction and inflammation leads to premature aging. The HIV/AIDS and Cancer Community Research Collaboration aims to assess and meet the needs of underserved and minority PLWHA who are at high-risk of premature aging.[7] Steps were taken to form focus groups, develop a needs assessment survey (NAS) and administer the NAS to 50 community HIV/AIDS providers. A Community Advisory Board was formed following criteria that included diversity in mission/services offered to PLWHA, populations served and geography in New York City. Only three of the 10 centers provided cancer-focused programming. The first focus group assessed cancer prevention. It was found that smoking cessation programs were in place, but cancer prevention programs were not due to barriers such as stigma, lack of resources and low priority. The common theme that arose from the different focus groups was that though there was interest in implementing cancer prevention programs, the agencies and cancer care providers needed more education about cancer and its impact on the PLWHA community as well as education on cultural competency; however, there was a fear of losing autonomy by participating in such research. Results from the community NAS showed that most organizations had alcohol and tobacco assessment and assistance programs as well as referrals for cancer screening. However, very few had mobile cancer screening methods or support groups for cancer patients. Most organizations did not have funding to support cancer-focused activities. Dr. Lubetkin concluded her talk with further description of the AIR trial, introduced by Dr. Burkhalter, a process that could be beneficial to AIDS service organizations in motivating PLWHA with respiratory feedback and motivational interviewing.

PUBLIC HEALTH PERSPECTIVES

The keynote presentation for day 2 was "Smoking Cessation in PLWHA: What Works?" by Raymond Niaura, PhD. The difference in survival between genders is equal, but there is 11-13 year difference between smokers and non-smokers in the general population.[18] Studies have shown that the survival curves of early quitters are very similar to non-smokers, with a 4 year gain in life expectancy to those who smoke until age 55, an important statistic for insurance and medicare purposes.[19] The higher prevalence of smoking in PLWHA as discussed throughout the conference is a public health emergency. HIV positive patients who are non-smokers have the same survival curve as smokers who are HIV negative. The combination of an HIV positive smoker accounts for the largest number of lost lives/year. According to a study on cardiovascular disease, smoking cessation causes tangible health benefits for PLWHA. Behavioral counseling and pharmacotherapies (nicotine replacement therapy [NRT], Chantix and Zyban) have been shown as effective interventions in the general population. In the PLWHA population, NRT with an increased amount of behavioral therapy was not more effective than NRT with less behavioral therapy. Group or cellphone counseling, however, was more effective than standard care.[20] Another study showed that using motivational interventions had no increased effect versus standard interventions while obtaining nicotine patches was predictive of success.[21] This was further elicited using a multiple mediation model.[22] In the AURORA study, a culturally targeted intervention for Latinos with HIV, NRT patch use during the intervention was a strong predictor of the outcome. The study did not provide any evidence that cultural tailoring is more effective than standard care, though.

In his presentation, Walter Royal, III, MD, spoke about "Cigarette Smoke Exposure and HIV-related Neurologic Disease Progression-Basic Mechanisms and Clinical Consequences". Smoking causes an increased risk of Alzheimer's disease, stroke and multiple sclerosis; interestingly, it causes a decreased risk of Parkinson's disease. There is an increased risk of multiple sclerosis among children of cigarette smokers. Smoking increases HIV-related morbidity and mortality, with infectious complications, lung diseases and increased risk of neurocognitive impairment. Smoking causes increased white blood cell counts and carbon monoxide that converts to carboxyhemoglobin, which produces reactive oxygen species that activate certain cell signaling pathways.[23] In addition, light to moderate smokers have increased CD4 and CD8 T cell counts while heavy smokers have increased CD8 but decreased CD4 counts. Nicotine from cigarettes suppresses lymphocyte proliferation and cytokine production, induces T suppressor cell activity, suppresses thymic T cell development, decreases antibody response and has many other damaging effects on the immune system. It is interesting that nicotine has been shown to improve attention performance in adults; however, abstinence from nicotine results in worsening and the effects of second hand smoke are extremely detrimental to children. HIV affects the brain directly through soluble inflammatory mediators, HIV proteins and other factors, resulting in a variety of HIV-related neurocognitive disorders. Studies have been conducted comparing control and HIV-1 transgenic rats.[24] The transgenic rat performed worse on the open field testing, showed increased T cell stimulation and decreased monocyte stimulation compared to the controls. There was increased cytokine secretion by splenic T cells resulting in inflammation while the splenic macrophages showed decreased interferon gamma (INFγ) and interleukin-1beta

and increased tumor necrosis factor alpha (TNFα) secretion in the transgenic rats. Mitogen-activated protein kinase pathways were also activated in transgenic rat brains. In addition, the dual oxidases (DUOX1) reactive oxygen species receptors were up-regulated in the transgenic model. In a rat model of cigarette smoking,[25] there was increased staining of class II major histocompatibility complex, increased cytokine expression and increased Nuclear factor erythroid 2-related factor 2 activation to reduce the damage by reactive oxygen species.[26] INFγ and TNFα responses were markedly increased in transgenic "smoked" rats, which also showed increased expression of brain vascular endothelial growth factor and cytokine expression. Wild type "smoked" rats showed an increase in DUOX1 receptors, whereas transgenic "smoked" rats showed decreased expression. Hence, understanding the mechanisms affected by smoke exposure may be useful in solving the complications that occur in PLWHA smoker sub-populations.

Yessenia Castro, PhD, presented the "Psychosocial Mechanisms of Smoking Abstinence among Smokers of Low SES". The smoking prevalence rate is almost half in those who earned only a general educational development and that rate drops as the education level increases. 31% of the population living below poverty status smokes, as opposed to 19% of those living above (CDC). This data indicates that the smoking rate is becoming increasingly concentrated in people of low SES. A study conducted on mechanisms linking SES and postpartum smoking relapse (a randomized control trial evaluating a treatment for reducing postpartum smoking relapse among women who quit smoking during pregnancy) used SES, negative affect, craving and agency as latent predictor variables. Specifically, negative affect, agency and craving were mediators of the SES-relapse relationship, while craving was found to be the direct pathway to relapse.[27] Another study titled "Reciprocal Relations among Mechanisms of Smoking Cessation", a longitudinal cohort study of low SES smokers in treatment, measured motivation, self-efficacy, positive affect, negative affect and craving. Of the multiple systematically hypothesized models, motivation and self-efficacy, self-efficacy and positive affect and negative affect and craving were all found to have reciprocal effects, affirming prominent drug treatment models; with only motivation and self-efficacy directly affecting smoking cessation, consistent with findings that motivational interviewing is beneficial.

The session ended with Subhash C. Chauhan, PhD, discussing "Smoking and Cervical Cancer Health Disparity". Cervical cancer is the second most common cancer among women, globally. Cervical cancer is associated with high risk human papillomaviruses (HPVs) and Gardasil vaccine targets those viruses. In South Dakota, 8.9% of the population is native American. The mortality of cervical cancer in African Americans and AI is thrice of the general population (CDC). The main issue is that of screening. HPV is more commonly detected in AI women and HPV positive AI women have higher rates of abnormal Pap tests. The smoking prevalence is also very high in the AI population. In addition, AIs have a higher percentage of HPV positive individuals in all age groups, highest in the 18-24 year range and also have multiple HPV genotypes. The natural progression of HPV infection begins with the viral particles invading cells and producing the E6/E7 oncogenes after integrating viral DNA into host DNA, then multiplying in multiple cells and cell layers before progressing to and resulting in invasive cancer. HPV E6 and E7 are required for the development of cervical cancer. E6 degrades p53 and E7 interferes with the retinoblastoma (Rb) tumor suppressor proteins, in addition to many other functions. Curcumin (diferuloyl methane), a compound found in turmeric, has many biological effects such as wound healing, anti-inflammation, anti-oxidation and immunomodulation.[28] Curcumin treatment[29] was found to suppress cervical cancer cell growth in monolayer. The compound induces apoptosis in cervical cancer cells through the caspase pathway, inhibits the motility of cervical cancer cells, represses HPV E6/E7 expression and restores the expression of p53 and Rb. Cigarette smoking is a risk factor for cervical cancer and the benzo[α]pyrene compound in cigarettes can be detected in the cervical mucus of women who smoke. Benzo[α]pyrene up-regulates the expression of HPV oncogenes, which is then suppressed by curcumin treatment. The benefits of curcumin have been demonstrated in a mouse model, in which treatment of orthotopic cervical tumors with curcumin showed visible decrease in tumor size.

BEST PRACTICES

The final session commenced with a talk titled "Brief Counseling Interventions for High-Risk Behaviors" by Scott T. Walters, PhD. Dr. Walters began with a statistic showing the length of intervention times as a direct positive contributor for tobacco quit rates at 1 year. The effectiveness of brief interventions in smoking is attributed to the feedback provided to the patients (lab tests, options and advice), the willingness of the patient to change (responsible behavior, self-confidence) and empathetic attitude.[30] Various intervention strategies, including the ones by dental hygienists, have shown very effective results in terms of quit rates. Dr. Walters presented a recently conducted study showing two 45 min interventions in a probation setting to have a positive effect on the drug and alcohol use in the participants. He then discussed the advantages of "treatment matching"– evidence based treatments/counseling as a specific

approach catered to special populations.[31] An interactive intervention where patient/client felt he/she was actually being heard and empathized with, without any judgment being passed about him/her seemed very important for the client to be honest and try to change. Further, the importance of training therapists to empathize with the patient was evident when more positive outcomes were observed with patients who had more empathetic therapists suggesting that therapists' empathy is a good predictor of how well the patient will do.[32] Dr. Walters finally delved into the importance of the motivational intervention process– encouraging and engaging the patient, focusing on the issue, planning a strategy and evoking the reason for the client to change and of what consequence that would be to the client.

The presentation by Damon J. Vidrine, DrPH, on "Smoking Cessation Treatment: A critical component of HIV/AIDS management" linked cigarette smoking to HIV/AIDS and the effects of cessation. Though AIDS diagnoses and death rates have not altered much in the last few years, the prevalence is steadily increasing, with black/African Americans having the highest diagnoses (CDC). 45-65% of PLWHA population is reported to be of low SES with depression and under the influence of drugs or alcohol. The poor health outcomes of smoking among the PLWHA is not only limited to poor quality-of-life and reduced responsiveness to antiretroviral treatment (HAART), but also results in increased mortality, with survival rates being highest in non-smokers and lowest in smokers.[33] Dr. Vidrine pointed to multiple studies that have shown the responsiveness of PLWHA to combined cessation treatments including NRT, motivational intervention, individual counseling, intensive group therapy and self-help. His group is actively involved in "Project Reach Out", an innovative intervention for HIV-positive smokers provided via telephone.[34] The main aim of this project is to compare the efficacy of this innovative technique to the standard of care and also to evaluate the role of motivation and other common attributes as mediators of smoking abstinence. This trial was randomized, conducted in Houston, TX and subjects were recruited using the CONSORT flow diagram. The cell phone intervention group got 11 phone calls over 3 months after quitting (motivational interventions), apart from the standard care; each call emphasizing different aspects of quitting and staying in a relapse-free state and tailored to the need of the individual participant. The sample was a good representation of the population in the area and significant differences were observed in the mean age of the participants between the groups. Alcohol and illicit drug use was about 30% and 40% in the past 30 days of recruitment, which was considered quite high. It was observed that the people in the cell phone group were 2.4 times more likely to maintain abstinence over 7 days. The overall conclusions from Dr. Vidrine's presentation were that the PLWHA were very receptive (about 90%) to smoking cessation, even if it was only for a 24 hour period, but the absolute quit rates were much lower; the innovative cell phone based method was effective only for the 3 month period and not over a sustained term (6 or 12 months). "Project STATE," a Medicaid waiver project in the pipeline, designed by Dr. Vidrine's group, is to assess the influence of HIV on smoking outcomes.

The concluding talk of this session, "Where do we go from here? Next generation treatment interventions" by Raymond Niaura, PhD, was on randomized clinical trials and personalized medicine. Treatment outcomes in terms of response prediction showed that among all the ethnic groups, abstinence over 6 months was higher in African Americans subjected to motivational enhanced treatment than standard of care, posing the need to tailor the interventions. Dr. Niaura stated that individual tailoring should cater to the racial/ethnic/culturally disparate populations and populations with unique needs (like, HIV/AIDS compared to other chronic illnesses). He suggested that sequential training is the optimal method to maximize the outcomes that could be achieved. In terms of treatment selection, matching the patient characteristics (initial) and adapting treatment to interim outcome (dynamic) were the two categorical personalized modalities. Pharmacogenetics, a model that customizes health care with medical decisions, practices and products tailored to an individual patient has led to better patient outcomes. Many complex and elaborate clinical algorithms have been considered for smoking cessation treatments in the past, based on randomized clinical trials.[35-37] The disadvantages in most of these could be overcome by multiphase optimization strategy, a multicomponent randomized trial, which includes preparation, optimization and evaluation.[38] The sequential multiple assignment randomized trial (SMART) is adaptive treatment strategies (ATS) tailoring time varying treatments for an operational clinical practice from both patients' and clinicians' view and questioning every critical treatment decision to modify individual variables during treatment and also modify the treatment itself. The advantages of ATS include heterogeneity in response to any treatment, improvement being marred by eventual relapse, tailoring multiple variables and enabling sequential treatments. The overall concept of the ATS is based on initial treatments monitored under responders and non-responders. The non-responders are then re-randomized to an enhanced treatment or augmented with the other regimen to facilitate enhanced positive patient outcomes.[39] There are few such ATS based trials for cancer therapy. A success story with the dynamic treatment regimen was seen in children treated for attention deficit hyperactivity disorder. Though, it

may seem that combining all the effective treatments and providing them as a package to every individual would be more efficacious, in reality, it is not since it will be very cost ineffective and the excessive treatment may lead to non-adherence and other complications. Subjecting the patient to the existing best therapeutic approach followed by the secondary and tertiary treatments may be an acceptable regimen but the disadvantage to this schema is that delayed therapeutic responses are not considered and so the most effective treatment (or positive synergistic sequential regimen) may simply be missed over the course or prescriptive effects, where specific symptoms that could be revealed by sequential treatments, may not be uncovered. Another example that Dr. Niaura showed to explain the importance of SMART was the study involving pharmacologic treatments for smoking in HIV positive smokers.[40] Since NRT did not show a very promising response and Chantix was a more efficacious drug, they wanted to test using ATS "what does one do when smokers fail to quit or relapse and what does one do when smokers quit". Building tailoring variables into this algorithm is quite critical and statistical techniques play an important role to facilitate this process and enable better analyses of the results. Though SMART has extensive potential, after the initial screening and study, it is imperative to complement it with conventional clinical trials to obtain more information on the final evaluation. The final thought that Dr. Niaura concluded with is that it's still a challenge in many ways to understand, treat and follow through with the subjects/patients and a lot of work is needed to be done to achieve the ideal situation.

CONCLUSIONS

The three highly informative and interactive sessions in the conference provided an excellent platform for researchers, clinicians and public health professionals to better understand the progress made in the past decades, the current scenario and the future challenges to be faced, from different perspectives, in the fields of smoking, HIV/AIDS and cancer. Many factors have been associated, either positively or negatively, with the disease/relapse predictions, but the complexity of the confounding variables associated with the primary factors is still quite colossal. Would differentiating between absolute or surrogate predictors better the prognosis? Will ensuring equitable care to all negate the disparities based on low SES, race/ethnicity and gender, thereby using only the molecular/genetic variables as the primary source of disparities? Will public education enhance the awareness to the extent of creating tangible differences in the current healthcare and disparity status/policies? These are some of the questions to which we are still seeking answers. It is important to comprehend that though very significant advances have been made in the field, we are still at the learning phase - trying to understand how to deal with affected individuals at a social level, trying to bridge the gaps causing disparities in access to care and treatment effectiveness, questioning the intricate complexities at the molecular level and/or taking advantage of the understanding to create new or better existing algorithms to enhance personalized therapies as cost effective and clinically efficacious alternatives. As Sir Isaac Newton said, if we need to see further, we have to stand on the shoulders of the giants.

ACKNOWLEDGMENTS

Funding for this conference was made possible (in part) by 1R13MD008150 and 5P20MD006882 (to JKV) from the National Institute on Minority Health and Health Disparities. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices or organizations imply endorsement by the US Government. Authors would like to thank the conference speakers for permitting them to document their presentations during the proceedings.

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How to cite this article: Rajendiran S, Kashyap MV, Vishwanatha JK. Intersection of Smoking, Human immunodeficiency virus/acquired immunodeficiency syndrome and Cancer: Proceedings of the 8 th Annual Texas Conference on Health Disparities. J Carcinog 2013;12:18.

Source of Support: 1R13MD008150 and 5P20MD006882 (to JKV) from the National Institute on Minority Health and Health Disparities.
Conflict of Interest: None declared.

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