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Cancer trials as opportunities to serve and learn from individuals with human immunodeficiency virus

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Since at least 2006, the National Cancer Institute (NCI) has had a clearly stated guideline[1,2]:

> Individuals known to be human immunodeficiency virus (HIV)-positive should not be arbitrarily excluded from participation in clinical cancer treatment trials. With effective antiretroviral therapy, individuals with undetectable HIV viral loads by standard clinical assays should generally be considered eligible for a study should they meet all the other eligibility criteria of the trial… HIV-infection should be considered as any other co-morbid condition that should be managed as per standards of care while a given patient is participating in clinical research.

Other groups have echoed this statement. For example, in 2017, the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group published recommendations on modernizing clinical trial eligibility and noted that the exclusion of persons living with human immunodeficiency virus (PLWHs) remained common.[3] Similarly,

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AUTHOR CONTRIBUTIONS

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in 2020, the Food and Drug Administration published specific guidance for cancer clinical trial eligibility criteria as they pertain to PLWHs; this guidance asked investigators to broaden cancer trial eligibility and pointed out that unnecessarily restrictive eligibility criteria may slow patient accrual, unfairly limit patient access, and lead to trial results that are not fully representative of treatment effects in the patient population for which that drug will ultimately be used.[4] How much attention have we in oncology paid to these advisements? Despite such entreaties, a survey of US oncologists in 2015 showed that 21% of physicians would not provide standard cancer treatment to PLWHs, and it revealed that provider-level factors are undoubtedly associated with the delivery of nonstandard cancer treatment to such patients.[5] This suggests that further creativity, policy changes, and multidisciplinary collaboration are needed to improve these patients' access to quality cancer treatment. We recently attempted to examine the NCI trial database for HIV data on trials for patients with cervical, anal, and oropharyngeal cancer over the last 20 years, and we found that there is minimal to no HIV-related information collected on NCI-sponsored trials. Specifically, we sought to examine human papillomavirus (HPV)–associated cancers in PLWHs treated in NRG trials and thus submitted an ancillary application aiming to explore Radiation Therapy Oncology Group (RTOG) 9811 and RTOG 0529 (anal cancer trials); NRG HN002, RTOG 0129, RTOG 0522, RTOG 0234, and RTOG 1016 (oropharyngeal cancer trials); and NRG GY002, Gynecologic Oncology Group (GOG) 165, GOG 219, and GOG 120 (cervical cancer trials). Unfortunately, our proposal was deemed not feasible because there has historically been minimal to no HIV-related information collected on NCI-sponsored trials. Specifically, the HIV status was not recorded for GOG 120, GOG 165, or GOG 219, and it was collected for NRG GY002 only because it was, reasonably, an exclusion criterion. Importantly, concomitant medications were also not collected in these trials. Similarly, no HIV or highly active antiretroviral therapy (HAART) regimen data were collected in RTOG 0129, RTOG 0234, RTOG 0522, or NRG HN002. More promisingly, RTOG 1016, the most recent of these head and neck trials, did collect the HIV status, and it accrued four PLWHs (out of 987). Although this does represent progress, and the relative proportion of the PLWHs enrolled in the study is potentially representative of the overall HIV prevalence in the United States (approximately 1.2 million), we nevertheless cannot exclude that disparities in access to care for PLWHs and provider bias and stigma surrounding an HIV diagnosis may have prevented more patients from enrolling in the study. As for the anal cancer trials, neither RTOG 0529 nor RTOG 9811 documented the HIV status or concomitant medications. It is important to note that most of these trials predated the NCI inclusion statement, but these findings have piqued our curiosity and compelled us to discuss how we as trialists may be able to do better. Similarly, appeals have recently been made to better collect information on the sexual orientation and gender identity of patients enrolling in cancer trials, with a recent American Society of Clinical Oncology survey showing that this information is collected less than half of the time despite the majority of respondents feeling that knowing this information is important.[6] Our aim in writing this article is to provide further education regarding why all NCI-funded studies for which PLWHs are eligible should include a special data report form through which important data of interest can be collected.

PLWHs have a two-fold greater risk of developing a non-AIDS-defining malignancy (NADM) in comparison with the general population; this includes NADMs associated with oncogenic virus infections, or viral NADMs.[7] In particular, HIV positivity is associated with an increased risk of persistent HPV infection at different anatomic sites, and this increases the burden of HPV-related cancers among PLWHs.[8] Women living with HIV have a higher risk of HPV infection, precancerous lesions, and cervical cancer, and this risk is inversely associated with the CD4 count.[9] Additionally, PLWHs have two- to three-fold higher odds of prevalent oral HPV infection in comparison with HIV-uninfected individuals and have an overall oral HPV DNA prevalence between 20% and 45%, with potentially oncogenic HPV subtypes found in 12%–26%.[10] There is evidence that HAART does not improve control of oral HPV infections in contrast to cervical HPV infections. Therefore, HPV-associated head and neck cancers will likely pose an increasing threat for immune-competent PLWHs as they live longer because of HAART.[10]

There are conflicting data regarding treatment and survival outcomes for PLWHs treated for NADMs. Even after controlling for known prognostic factors, many studies have shown worse outcomes for these patients in comparison with the general population, even in developed countries.[11,12] Other studies, however, have shown no evidence of disparities in survival between HIV-positive patients and the general population. For example, Trickey et al.[13] conducted a collaborative analysis of cohort studies (the Antiretroviral Therapy Cohort Collaborative) in the United Kingdom and France and found that survival was worse for PLWHs diagnosed with Hodgkin disease than the general population; however, for cervical, head and neck, liver, and lung cancer, there was no difference in outcomes. This study, published in 2020, was the first to analyze cause-specific mortality among PLWHs diagnosed with a range of specific cancers and spanning multiple countries, and the authors concluded that the publication and dissemination of such information may encourage PLWHs to be more proactive in being screened for cancer. Interestingly, they also noted that the proportions of deaths due to an NADM were 39% after a viral NADM and 60% after a nonviral NADM.

Coghill et al.[14] published a Surveillance, Epidemiology, and End Results database study in *JAMA Oncology* in 2019, which retrospectively evaluated approximately 308,000 patients, all at least 65 years old, with colorectal, lung, prostate, or breast cancer. The authors found elevated cancer-specific mortality rates for breast and prostate cancer but not for colorectal or lung cancer in PLWHs. Worse outcomes in HIV-positive patients with breast cancer have also been reported by others.[11]

The majority of the current literature on the issue of cancer in PLWHs concludes that future work should evaluate the association between HIV and cancer-specific mortality for different cancer types. There is an unmet need for studies using more detailed cancer treatment data and biological measurements of immunosuppression, particularly in the era of effective HAART, as the number of PLWHs who are diagnosed and are being diagnosed with cancer increases.[15]

For the most part, modern cancer clinical trials do not exclude PLWHs, and there are now organizations such as the AIDS Malignancy Consortium, an NCI-supported clinical

trials group, that seek to study and develop better therapies for malignancies in PLWHs. The AIDS Malignancy Consortium currently has five studies under its HPV working group: four studying anal lesions and one studying cervical lesions. These studies are investigating such interventions as vaccine therapy, outcomes research, immunotherapy, excisional techniques, and topical chemotherapy.[16] Despite such progress, however, most trials continue to miss important opportunities to learn about how cancer behaves in PLWHs. As discussed previously, we attempted to examine HIV data on the NCI-sponsored trials in patients with HPV-associated cancers. To reiterate, neither RTOG 0529 nor RTOG 9811 (anal cancer trials) collected the HIV status, HAART regimen data, or quality-of-life end points. The same is true of GOG 0120, GOG 0165, and GOG 0219 (cervical cancer trials) as well as RTOG 0129, RTOG 0234, RTOG 0522, and NRG HN002 (head and neck cancer trials that included oropharyngeal cancer). RTOG 1016, a trial specifically for patients with HPV-related oropharyngeal cancer, did collect the HIV status; four of the 987 enrolled patients were PLWHs.

We continue to learn more about the interplay between the immune system and cancer biology, and immunotherapy drugs are increasingly being used in cancer therapy; however, these advances raise as many new questions as they provide answers. Immunotherapy trials have historically excluded PLWHs,[17–20] although this trend does seem to be changing, as emerging evidence suggests that there are no safety signals and that efficacy approaches that achieved in patients without HIV infection.[21] NRG HN005 and NRG GY017 are representative of these positive changes. Even within trials that do allow PLWHs to enroll, however, there is clearly room for strategic improvements in data collection. Within large, high-quality cooperative group cancer clinical trials, particularly with respect to PLWHs, this would allow the possibility of important insights. First, it would give us a clearer picture of the relationship between HIV and cancer. Are there truly disparities in outcomes, and if so, what are the reasons behind them? The HIV infection itself? A propensity for more aggressive cancer biology? Differences in treatment tolerability and compliance? Diminished access to timely diagnosis and treatment due to socioeconomic factors[11]? To date, studies describing the relationship between HIV and cancer have not adjusted in detail for the treatment type, and they lack granular data despite evidence of suboptimal cancer therapy in the setting of HIV.[14] Although the contribution of PLWHs in any one trial may be limited, the cumulative analysis of such patients has the potential to answer some very important questions, but only if the relevant information is collected. To this point, the collection and analysis of data obtained in the setting of randomized trials would offer us what these other analyses have not: detailed, high-quality cancer treatment data and long-term follow-up; standardized, best available treatment; and expert multidisciplinary collaboration. This will be possible only with additional data collection within the context of the trials, including the HIV status and viral load, biological measurements of immunosuppression (e.g., the CD4 T-cell count), and HAART regimen data. In addition, drug repurposing for anticancer therapies is a very active area of research[22,23]; in particular, protease inhibitors as antineoplastics are the subject of several ongoing clinical trials in various advanced solid tumors, including vulvar cancer (NCT04169763), prostate cancer (NCT05036226), and cervical cancer (NCT03256916), as well as relapsed or refractory multiple myeloma (NCT03829020). In one published

study of cervical cancer, the combination of nelfinavir with standard chemoradiation has demonstrated promising activity, with 10 of 11 patients remaining disease-free at 50 months.[24] Simply documenting medication lists for patients enrolled in cooperative group trials would thus open up the opportunity to easily investigate exceptional responses; this pertains to HAART regimens and medications in general. The authors propose that all NCI-funded studies for which HIV-positive patients are eligible should include a special data report form for HIV-positive patients.

As exciting as these areas of potential discovery are, these data are also worth collecting so that we can ask ourselves very basic but very important questions. For example, how well are we doing at getting patients living with HIV into trials for which they are eligible? How well do they do on the trials? Is their experience of toxicity and quality of life different from the experience of HIV-negative patients? We owe it to our patients to attempt to answer these questions with the goals of improving education and advocacy and effecting policy changes.

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CONFLICTS OF INTEREST

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