Antiretroviral therapy prescribing in the real-world and impact on cancer risk

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In the 1980s, the onset of cancers, such as Kaposi sarcoma and non-Hodgkin lymphoma (NHL), and high cancer-associated mortality in young men portended the emergence of HIV [1]. In the last 40 years, combination antiretroviral therapy (ART) regimens that were developed to treat HIV have decreased the incidence and favorably impacted the prognosis of these cancers in HIV-positive populations. With the introduction of ART from 1996, the overall survival of people with HIV (PWH) improved with evidence of decrease in the incidence of both Kaposi sarcoma and NHL over time, though this risk remains elevated as compared with the general population [2]. In the early 2000s, as use of ART became widespread, the benefit of early ART initiation at the time of initial HIV diagnosis rather than at specific $CD4^+$ T-cell counts thresholds and its impact on historically termed 'AIDS-defining' malignancies or infections remained an outstanding question. By 2015, the seminal INSIGHT-START randomized controlled trial demonstrated that early initiation of ART led to a 72% relative reduction in AIDS-related events, which included Kaposi sarcoma and NHL [3]. Though this study, other trials and observational studies have shown an effect of ART on decreasing specific cancers [4–8], the broad impact on real-world practices of ART prescribing on cancer incidence (including virus-unrelated cancers or malignancies associated with aging) have not been fully delineated.

In this issue of *AIDS*, Horner *et al.* evaluate the association between individuals in an HIV registry, their ART prescribing and usage patterns with the HIV/AIDS Cancer Match registry in Texas from 2008 to 2015 [9]. The prescription dataset used within this study included Medicaid, Medicare and private insurance claims, which covers 93% of prescriptions dispensed within the United States. Within the state of Texas, 63 694 PWH (39% non-Hispanic Black individuals) were evaluated for virus-associated and virus-unrelated malignancies. To assess the effect of ART on cancer risk, the authors define an exposed ART population, where individuals receiving at least 1 month of ART prescriptions were assumed to have subsequent months prescribed. Those who were classified unexposed, or unknown were individuals who had other medications were prescribed but not ART or provided less effective or incomplete combinations of ART. This broad assumption of exposure to ART approximated an intent-to-treat paradigm for the analyses and the impact of ART on cancer risk.

In this real-world evaluation of the use of ART in Texas, which represents an area with high prevalence of HIV within the United States, the authors assume that all prescribed medications were taken as directed, therefore, an assessment of adherence could not be fully evaluated [9]. The data may also tangentially address the socioeconomic challenges in care among PWH in this area. The overall median proportion of follow-up time on ART was 21% and 54% in the exposed category, indicating the myriad of challenges that this population may face with continuity of their medical care. Though the prescription database covers Medicaid and Medicaid, it may not sufficiently cover prescribing patterns for patients who are within the low income uninsured and under-insured categories who receive ART with Texas HIV Medication Programs. Despite these conditions of real-world data within the study, a broad number of cancers were identified.

Patients with ART-exposed status within this study had 50–60% reduction in Kaposi sarcoma and NHL risk as

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compared with those who were unexposed [9]. There was also a 30–40% decrease in liver and anal cancers in those who were ART-exposed. Other cancers that continue to increase among PWH, such as lung cancer and Hodgkin lymphoma, were not different between exposed and unexposed groups. The study is unique for the inclusion of a large number of patients, long follow-up time of (median 76 months) and cancer risk among PWH in a real-world setting where ART-prescribing patterns could be considered, including an unexposed cohort where HIV therapy was unfortunately not received by PWH in the modern ART era. As compared with other studies investigating the association between ART and cancer risk, the magnitude of risk reduction observed in this study was more conservative as compared with data from Silverberg *et al.* [5] demonstrating a 75% decrease in Kaposi sarcoma risk among those with early ART initiation in the North American HIV cohort study (NA-ACCORD). This difference was likely because of the misclassification of ART exposure in the study by Horner *et al.* as those with unexposed or unknown status with limited ART data biased cancer risk towards the null. With regards to other virus-associated cancers, though decrease in anal cancer was observed, cervical cancer risk, also caused by human papillomavirus, was not different. This is discrepant from a large cohort study from France demonstrating a 50% decrease in cervical cancer with use of ART for more than 6 months [10]. Though half the patients in the cohort studied by Horner *et al.* had HIV for 3 years or more, the effect of ART on the longitudinal $CD4^+$ T-cell count dynamics and HIV viremia and its association with the onset of these cancers has not been included. This is the benefit of observational studies that have controlled and closely followed exposure to ART and have more detailed information on the impact of $CD4^+$ T-cell count and HIV viral suppression on the onset of cancers [4–6]. The longitudinal relationship between several factors such as viral control, immunosuppression, inflammation and how these factors change at HIV diagnosis, ART initiation and cancer onset require further investigation.

The lack of impact observed between ART-exposed and virus-unrelated cancers may be because of additional factors related to ageing, metabolic syndrome, other exposures, such as smoking, that may contribute to causation. The benefit of cancer prevention strategies for virus-unrelated cancers, specifically for lung cancer, which remains at high risk compared with the general population [11] and contributes to cancer-related mortality among PWH needs further investigation [12]. In addition to ART prescribing, real-world studies need to also consider the uptake and benefit of other preventive measures available to the general population, such as cancer screening and vaccination to determine the impact of cancer prevention approaches for PWH with elevated cancer risk as they age.

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Conflicts of interest

There are no conflicts of interest.

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