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Clinical and Scientific Challenges in HIV-associated Malignancies

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Introduction

For people living with HIV, recent years have seen striking advances in the range of antiretroviral therapies available, our understanding of the optimal application of these therapies in clinical practice, and their availability even in less resourced settings [1]. These advances have translated into continuing improvements in the proportion of people with HIV who are receiving effective antiretroviral therapy (ART), and reductions in the burden of morbidity and mortality caused by HIV globally [1].

Notwithstanding this exceptional progress, even with effective ART people with HIV remain at increased risk of many medical comorbidities. Most prominent among these is an elevated risk of cancer. The risk of malignancy remains approximately double that of the general population and, in both resource rich and resource limited settings, cancer is now the leading cause of death for people with HIV. While cancers associated with severe immunosuppression are less common in the modern era, the risk of many malignancies including most lymphomas, lung cancer, and anal cancer remains substantially elevated as Sheils et al describe in this issue [2]. This excess burden of cancer is important not only for its human impact on people living with HIV but also for its resource implications for health systems and its social and economic impact on communities.

The fourteen reviews in this issue of *Current Opinion in HIV and AIDS*, entitled “Clinical and Scientific Challenges in HIV-associated Malignancies”, are selected to reflect the breadth of clinical science currently underway in HIV-associated malignancies. They are grouped thematically, covering, in the first section epidemiology and the foundational role of ART; in the second, advances in prevention and therapy of specific HIV-associated malignancies; and in the third, broader issues in the field including selected special populations. In this editorial, we discuss the implications of the advances described in this issue as they apply in resource rich and resource limited settings, and consider the ways in

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which work in HIV-associated malignancies can help inform and develop clinical care and scientific studies more broadly.

Recent Achievements and Advances in HIV-associated Malignancies

i. Prevention Strategies—Mitigating the increased risk of malignancies in people with HIV by developing new prevention strategies is of key importance. As is apparent from the articles in this issue, this area has seen substantial recent progress. Advances include optimized therapeutic strategies for HIV itself and for several concurrent viral infections implicated in cancer development, as well as an increased awareness of the role of behavioral modification and screening for many solid tumors.

Effective delivery of ART is fundamental in reducing the risk of malignancy in people with HIV. Borges *et al.* summarize the ongoing evolution of our understanding of the impact of ART on cancer development, including The Strategic Timing of Antiretroviral Therapy (START) trial [3,4]. START demonstrated the substantial impact of immediate ART initiation, even at well-preserved CD4 counts, in preventing cancer. The immediate ART group showed a significant reduction in the composite primary endpoint of serious events and deaths. This was driven in large part by a reduction in new malignancies, particularly those related to infection, in the immediate ART arm [4,5]. The mechanism of this protective effect is not completely clear, but may reflect the impact of inflammation and of unrecognized immune deficits on cancer development.

Therapeutic advances in inhibiting other viruses linked to the pathogenesis of cancers in HIV should have a further impact in preventing HIV-associated malignancies. For those people with HIV who are also Hepatitis C (HCV) infected, new direct acting antiviral agents for HCV are likely to reduce the incidence of hepatocellular carcinoma, as Abou-Alfa *et al.* report [6]. Similarly, as Palefsky *et al.* describe, the availability of effective vaccines against human papillomavirus (HPV) has the potential to reduce the impact of HPV-associated malignancies, including cervical, anogenital and some oropharyngeal cancers [7]. Unfortunately, in part due to cost, vaccine roll out in resource limited settings, where the burden of HPV-associated malignancies is highest, remains very limited. Uptake in many well resourced settings has also fallen short of goals, especially in boys. Data on the persistence of vaccine-conferred HPV immunity and the long term impact on cancer rates are required, as are better interventions for established high grade HPV-associated intraepithelial neoplasia.

Supporting these medical interventions is the development of community based campaigns to target other modifiable risk factors for cancer. Key among these is tobacco cessation, as people with HIV continue to report higher rates of smoking than the general population. Sigel *et al.* describe the importance of this in the observed elevated risk of lung cancer among people with HIV [8]. They further outline recent data supporting a possible role for CT screening for lung cancer in selected, high risk patients with HIV [9]. Given evidence that people with HIV are less likely to receive standard preventive care, including cancer screening such as colonoscopy, uptake of screening measure like this is likely to require investments in patient and practitioner education and clinical infrastructure.

ii. Therapeutic Strategies—Key recent therapeutic advances for established malignancies include studies establishing the applicability of standard cancer therapies in people with HIV and the development of immune modulatory and antiviral strategies that respond specifically to the pathogenesis of certain HIV-associated malignancies. There is also a major effort underway to apply these therapeutic advances in resource limited settings, including studies of Kaposi sarcoma and lymphoma in sub-Saharan Africa using chemotherapy regimens tailored to local infrastructure with close monitoring of safety and deliverability (NCT1435018 and NCT1352117).

Carbone *et al.* summarize the substantive recent advances in therapy of HIV-associated lymphomas [10]. Studies led by the U.S. National Cancer Institute (NCI) intramural program and by the NCI-sponsored AIDS Malignancy Consortium (AMC) have shown excellent results with standard therapies for HIV-associated lymphomas, both in initial therapy and at later stages when transplant is required. The NCI and AMC studies of EPOCH chemotherapy in diffuse large cell lymphoma and more recently in Burkitt lymphoma demonstrated excellent efficacy with adverse events within expectations [11,12]. In the AMC study, autologous stem cell transplantation was similarly found to be safe and efficacious when used for standard indications in patients with HIV-associated lymphomas [13]. Taken together, these studies establish for this key group of HIV-associated malignancies that standard therapies are safely deliverable, with outcomes comparable to those in the non-HIV-infected population. An ongoing study of brentuximab vedotin with chemotherapy in newly diagnosed advanced HIV-associated Hodgkin lymphoma may well do the same for that malignancy (NCT1771107).

Defective immune surveillance of concurrent infection with oncogenic viruses is a key determinant of the development of many HIV-associated malignancies. Immune targeted anti-cancer agents may thus be particularly useful in this area. As Yarchoan *et al.* describe, studies in Kaposi sarcoma with the immune modulatory agents pomalidomide and lenalidomide have each demonstrated good efficacy and tolerability, and with pomalidomide detailed immunologic correlates supported at least in part an immunologic mechanism of action [14, 15]. Follow up studies of pomalidomide alone and in combination are planned, including in sub-Saharan Africa. Further studies are also envisaged exploring pomalidomide and related agents in certain viral lymphomas and other virally driven malignancies. Safety studies of immune checkpoint inhibitors alone (NCT2595866) and in combination (NCT2408861) in people with HIV-associated malignancies are also underway, and include patients with viral malignancies. Direct targeting of oncogenic viruses or their cellular targets may also be possible in certain HIV-associated malignancies, as demonstrated by a pilot study in multicentric Castleman disease [16]; other agents with direct viral targets including nelfinavir are now also entering clinical trials in selected viral malignancies.

Work continues to establish specific approaches for people with HIV with common solid tumors including lung, anogenital, and hepatocellular malignancies [6–8]. As new therapeutic modalities are rapidly emerging for the general population in these and many other solid tumours, ongoing developmental therapeutic studies hold the promise of establishing clear safety and tolerability data to guide clinical care in people with HIV. Skin cancers, including several rare tumor types, are also over-represented in people with HIV,

especially in less resourced settings, and Mauer *et al.* describe new therapeutic approaches to these, including the potential of less toxic local therapies [17].

Key Challenges and Opportunities in HIV associated malignancies

i. Resource rich settings—In resource rich settings, many of the current key clinical and scientific challenges in HIV-associated malignancies arise from the abundance of emerging therapies for cancer, and the consequent need to identify their safety and applicability in people with HIV-associated malignancies. Survival rates following cancer diagnosis for most major malignancies, including those over-represented in people with HIV, have greatly improved in the last decade [18]. It is crucial that these advances are also realized by groups disproportionately affected by cancer, including those with HIV.

As Suneja *et al.* describe, disparities in cancer treatment persist for people with HIV even where they present with curable and early stage malignancies [19]. These sobering data highlight the need not only to provide clinical trial data for people with HIV and cancer, but to understand and tackle barriers to implementation of optimal care in the community. Even within well resourced settings, certain populations including women, children, and those who are economically or socially marginalized face particular challenges that in many cases require targeted responses. For women, Chiao *et al.* describe the importance of cancer screening and the specific burden of malignancies including those caused by HPV, and the increasing importance with an aging population of common solid tumors including breast cancer [20]. Similarly, for children with HIV, Bohlius *et al.* outline both the distinctive pattern of tumors that occurs, including certain rare viral tumors, and the pressing need for more research including clinical trial data [21].

Notwithstanding the exemplary trials described here, providing high quality clinical trial data for people with HIV is a continuing challenge. As Little reports, people with HIV are routinely excluded from cancer clinical trials, in part due to sponsor concerns about the complexity of their medical condition [22]. Efforts to expand and modernize eligibility criteria and to promote a more nuanced approach to the eligibility of HIV infected people are ongoing. For many emerging agents, including immunotherapies and some targeted agents, there are legitimate concerns about differential susceptibility to toxicity, pharmacological interactions even with modern ART, and perhaps differential efficacy. Collaborative groups focused on HIV-associated malignancies, including the NCI AMC, thus play a critical role in undertaking targeted studies of key emerging agents in people with HIV to ensure that fundamental safety and pharmacokinetic data are available. These data will be necessary to support inclusion of people with HIV in definitive late stage trials. HIV-malignancy focused groups are also essential in leading studies in rarer diseases closely associated with HIV-infection which might not otherwise be studied [22,23].

The development of biomarkers and predictive strategies to identify those with HIV who are at highest risk of malignancy for surveillance or intervention is a further critical goal. This may best be served by incorporating biomarker discovery and validation studies in clinical trials and observational cohorts of the general HIV-infected population. Such studies have already provided fundamental insights into markers of normal physiology, including IL-6 and D-dimer, that are perturbed in treated HIV infection in ways that influence the risk of

comorbidities including cancer [24]. Better tools, however, are still required to identify those people with HIV who are at highest risk of malignancy, and potentially tailor interventions.

ii. Resource Limited Settings—In resource limited settings, the current challenges are more fundamental and vary substantially between countries and regions. The challenges that Gopal *et al.* outline in sub-Saharan Africa are shared to some degree across many resource limited settings, though there may be specific issues at each local level [25]. There exists in many settings a complex and interrelated set of barriers to progress in HIV-associated malignancies, with minimal epidemiological data concerning incidence and outcomes of malignancies, limited diagnostic capabilities, and limited cancer care infrastructure with, in some cases, minimal links to loci of HIV care. The ability to maintain and expand the current level of ART provision, which as we have seen is critical in preventing HIV-associated malignancies, is also under threat [1]. Importantly too, as recent data from Malawi have demonstrated, the conceptual understanding of cancer and its treatment in many populations can differ greatly from that in resource rich settings, where cancer is a common topic of discussion in general media [26]. Population and practitioner education will thus need to proceed in parallel with infrastructure development in order for clinical advancements to be achieved.

Notwithstanding these challenges, a unique opportunity is emerging in many resource limited settings, including Africa and Asia, to extend the established clinical and research infrastructure developed for ART rollout to support other important areas including the study of HIV-associated malignancies. The collaboration in sub-Saharan Africa of the U.S. National Institute for Allergy and Infectious Diseases (NIAID) AIDS Clinical Trial Group sites with the NCI AMC to support studies in HIV-associated malignancies illustrates the potential of this approach. Fellowships, exchanges, and similar training programs will be essential to ensure these collaborations deliver not only scientific outcomes but improvements in clinical and research capacity. Of course many difficulties remain, including a segregation of clinical and research funding. This renders integrated institutional models that embed clinical research into clinical care difficult to achieve.

iii. Scientific Opportunities—The nature of the pathogenesis of many HIV-associated malignancies also provides outstanding opportunities to undertake translational scientific studies in order to answer fundamental questions about immunity, oncogenesis, and viral pathogenesis. Worldwide, approximately 18% of all cancers are caused by infectious agents; the majority of which are attributable to seven human tumor viruses [27]. Studies in people with HIV, where these cancers are over-represented, will continue to provide fundamental insights into viral pathogenesis, oncogenesis, and implicated human cellular pathways [28,29]. The key role of immune deficiency in the pathogenesis of HIV-associated malignancies may also provide a unique window through which to better understand the immune surveillance of malignancy more generally. Conversely, as Rasmussen *et al.* describe, immune modulatory anti-cancer agents including checkpoint inhibitors, through their ability to perturb cells implicated in the HIV reservoir, can provide insights into mechanisms of HIV persistence and perhaps provide means of its eradication [30].

Developing a more globally integrated research infrastructure in HIV-associated malignancies, perhaps modelled on the achievements of international clinical trial and epidemiological collaborations in HIV, could support these scientific opportunities. In particular, international networks to support clinical trial accrual (as between the NCI AMC and sites in Australia and France) can accelerate progress while also improving patient access to promising investigational agents, as can epidemiological collaborations such as the National Institutes of Health IeDEA network. There is also a need for clinically annotated biorepositories reflective of the global variation in HIV-associated comorbidities, either as stand-alone population-based resources or within trials and cohorts.

Conclusions

An unexpected occurrence of cancers in young men in New York and San Francisco was one of the earliest harbingers of the AIDS epidemic, and, after thirty years of progress in HIV and cancer research, an elevated risk of malignancy remains a defining feature of HIV infection. Together, the authors of the reviews in this issue have made substantial contributions to our understanding of HIV-associated malignancies. Their writings show how the steady pace of advancement in prevention, therapy, and delivery of care is providing better tools to reduce the impact of HIV-associated malignancies and improve patient outcomes. HIV-associated malignancies are also uniquely situated at the intersection of virology, oncology, and immunology. The articles in this issue also show the many ways in which the study and care of this group of diseases can provide a platform from which to improve our understanding of each of these fields.

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References

1. The Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS by the numbers 2015. United Nations; Geneva: 2015.
2. Shiels M, Engels E. Evolving epidemiology of HIV-associated malignancies. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
3. Borges AH. Antiretroviral Therapy and Cancer Risk in People with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
4. The INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *New England Journal of Medicine*. 2015; 373:795-807. [PubMed: 26192873]

5. Borges ÁH, Neuhaus J, Babiker AG, et al. Immediate antiretroviral therapy reduces risk of infection-related cancer during early HIV infection. *Clin Infect Dis*. 2016 (Epub ahead of print).
6. Abou-Alfa G. Hepatocellular Carcinoma in People with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
7. Palefsky J. HPV and Associated Malignancies in People with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
8. Sigel K, Makinson A, Thaler J. Lung Cancer in Persons with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
9. Makinson A, Eymard-Duvernay S, Raffi F, et al. Feasibility and efficacy of early lung cancer diagnosis with chest computed tomography in HIV-infected smokers. *AIDS*. 2016; 30:573–582. [PubMed: 26829006]
10. Carbone A, Volpi CC, Gualeni AV, Gloghini A. EBV-associated Lymphomas in People with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
11. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood*. 2010; 115:3008–16. [PubMed: 20023215]
12. Dunleavy K, Pitaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. *New England Journal of Medicine*. 2013; 369:1915–25. [PubMed: 24224624]
13. Alvarnas JC, Le Rademacher J, Wang Y, et al. Autologous hematopoietic cell transplantation for HIV-related lymphoma. *Blood*. 2016; x:xxx-xxx.
14. Goncalves P, Ziegelbauer J, Uldrick T, Yarchoan R. Kaposi-Sarcoma Herpes Virus Associated Cancers and Related Diseases. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
15. Polizzotto MN, Uldrick TS, Wyvill KM, et al. Pomalidomide for symptomatic Kaposi sarcoma in people with and without HIV. *Journal of Clinical Oncology*. 2016; x:xxx-xxx.
16. Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. *Blood*. 2011; 117:6977–86. [PubMed: 21487108]
17. Mauer T, Coghill A, Suneja G. Skin Cancers in People with HIV. *Cancer Care Disparities in People with HIV in the United States*. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
18. U.S. National Cancer Institute. Annual Report to the Nation on the Status of Cancer. U.S. Department of Health and Human Services; Washington DC: 2016.
19. Coghill A, Suneja G. Cancer Care Disparities in People with HIV in the United States. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
20. Chiao E. Malignancies in Women with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
21. Bohlius J. Malignancies in Children with HIV. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
22. Little R. Cancer Clinical Trials in Persons with HIV Infection. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
23. Polizzotto MN, Uldrick TS, Wyvill KM, et al. Clinical Features and Outcomes of Patients With Symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-associated Inflammation: Prospective Characterization of KSHV Inflammatory Cytokine Syndrome (KICS). *Clin Infect Dis*. 2016 Mar 15; 62(6):730–8. DOI: 10.1093/cid/civ996 [PubMed: 26658701]
24. Boulware DR, Hullsiek KH, Puroon CE, et al. Higher levels of CRP, D-dimer, IL-6 and hyaluronic acid before initiation of antiretroviral therapy are associated with increased risk of AIDS or death. *J Infect Dis*. 2013; 207:1637–46. [PubMed: 23468056]
25. Chinula L, Moses A, Gopal S. HIV-associated malignancies in sub-Saharan Africa: progress, challenges, opportunities. *Current Opinion in HIV and AIDS*. 2017; 1:xxx-xxx.
26. Gopal S. Moonshot to Malawi. *New England Journal of Medicine*. 2016; 374:1604–1605. [PubMed: 27119235]
27. International Agency for Research in Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. International Agency for Research in Cancer; Geneva: IARC; 2012.

28. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994; 266:1865–9. [PubMed: 7997879]
29. Simonetti FR, Sobolewski MD, Fyne E, et al. Clonally expanded CD4+ T cells can produce infectious HIV-1 in vivo. *Proc Natl Acad Sci*. 2016; 113:1883–8. [PubMed: 26858442]
30. Rasmussen TA, Anderson JL, Wightman F, Lewin SR. Cancer Therapies in HIV Cure Research. *Current Opinion in HIV and AIDS*. 2017; 1:xxx–xxx.

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