Clinical Infectious Diseases

EDITORIAL COMMENTARY

Screening for Anal Cancer in the Population Living With Human Immunodeficiency Virus: A Step Closer?

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Human immunodeficiency virus (HIV) infection is the major risk factor for a 50-fold incidence increase of invasive anal squamous cell carcinoma (IASCC), especially among men having sex with men (MSM) [1]. IASCC is itself largely caused by an infection with 1 of the same oncogenic mucosal human papillomavirus (HPV) genotypes causing various other oro-genital cancers: in particular, cervical cancer [2]. Given the mounting evidence that HPV vaccination is preventing cervical cancers, and possibly other HPV-related cancers, as well as precursor lesions and infections, we should eventually see a major reduction in the incidence of IASCC among the vaccinated population, and probably beyond by herd immunity [3, 4]. However, this will take a few decades and a wide implementation of HPV vaccination recommendations. Clearly, an alternate preventative approach to IASCC continues to be highly desirable, particularly in the population living with HIV.

Considerations about the epidemiology and pathogenesis of HPV anogenital infections and initial cost-effectiveness analyses led to the outline of a screening strategy inspired from the established and successful use of cervical cytology (Pap smear) to prevent cervical cancer [5]. Even if the precise screening algorithms remain to be optimized [6], the concept was put into practice by many HIV clinics throughout the United States and elsewhere, but is typically not yet part of national guideline recommendations. Almost 20 years later, the critical question of whether this approach has reduced the incidence of IASCC in the population living with HIV still has no appropriate answer. After it was introduced for mass screening of cervical cancer in 1952, the cervical Pap smear was not submitted to prospective, randomized studies [7]. Instead, it took the accumulation, until the early 2000s, of many observational studies of increasing quality and scope to fortunately lift all doubts about its effectiveness [8]. The prompt and proper collection of evidence is imperative. This is why the work by B. Revollo and colleagues [9] in the present issue of the journal is an important, if initial, attempt at demonstrating the usefulness of anal screening for the prevention of IASCC in HIV subjects.

These authors retrospectively analyzed a cohort of individuals living with HIV, followed between 2005 and 2016 at their reference HIV Unit of the Hospital Germans Trias I Pujol in Barcelona, Spain. Subjects living with HIV, including MSM, men having sex with women (MSW), and women, were followed prospectively at this single institution. They were all offered participation in a cytology-based anal cancer screening program that allowed the periodic triaging of patients to high resolution anoscopy, biopsy, and treatment by infrared coagulation or surgery of high-grade anal intraepithelial neoplasia, which is the precursor lesion of IASCC. Patients suitable for analysis who accepted screening (n = 1691) were compared to those who declined or dropped out of the screening program after less than 6 months (n = 1420). The endpoint was the incidence of IASCC. The authors observed 2 IASCCs in the screening group (incidence rate of 21.9 per 100 000 person-years), with both in MSM; in comparison, there were 8 IASCCs in the no-screening group (incidence rate of 107.0 per 100 000 person-years), with 4 among MSM, 2 among MSW, and 2 among women. The hazard ratio after a propensity score adjustment was 0.17 (95% confidence interval 0.03–086). This suggests that cytologic screening offers a benefit for the prevention of anal cancer.

It is significant that neither of the 2 cases of IASCC in the screening group were identified directly by the screening strategy itself, but instead by the presence of symptoms or a mass, presumably detected by digital anorectal examination, which is an established practice. Nevertheless, both patients had hemorrhoids, which may have complicated the screening. Also, in the nonscreened group, the mortality rate was high (5 out of 8 patients). This would be a striking observation if this was the consequence of the anal cancer, but that information was not provided.

Several notes of caution are in order regarding these results and their impact.

Received 13 August 2019; editorial decision 16 August 2019; accepted 23 August 2019; published online September 4, 2019.

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Clinical Infectious Diseases® 2019;XX(XX):1–3

DOI: 10.1093/cid/ciz836

This was an observational study and the patients self-assigned to 1 of the 2 groups, choosing whether to be screened or remain unscreened. For reasons that are not obvious, the IASCC incidence in the unscreened group was particularly high, at about twice the rate that has been previously observed in persons living with HIV in North America [1]. When baseline variables known to potentially affect the incidence of IASCC—such as risk group (MSM and MSW), baseline CD4+ cell count, CD4+ cell count nadir, CD4+ cell count nadir less than 200, and HIV viral load—were compared, the differences between the 2 groups were highly statistically significant. The noncomparability of groups at baseline is always a concern in observational studies, when randomization is not present to provide a relative protection against the effect of confounding variables. To correct for this problem and make the 2 groups more comparable, the authors used propensity scores, which is a standard approach. Propensity scores can be used in a large variety of ways that can be regrouped in 3 general strategies [10]. They can be used to (1) stratify the 2 groups into more comparable subgroups; (2) match each member of a group to a comparable member of the other group; or (3) create a covariate whose values, the propensity scores, are used in a final regression analysis, which was the approach used here. The advantage is that there can be many confounding variables that need to be adjusted, which could affect the statistical power and reliability of the analysis. When entered as predictive factors in a logistic regression model, they produce a single variable: the propensity scoring. Guidelines have been proposed for the usually defective but important reporting of propensity score analyses [11].

There are indeed limitations to these techniques. For example, the validity of logistic regression is sensitive to extremely high correlations among the predictive factors. Baseline CD4+ cell count, CD4+ cell count nadir, CD4+ cell count nadir less than 200, and even HIV viral load are undoubtedly correlated variables, but the authors did not comment on this issue. Another concern is the dissimilar and multimodal distributions of the propensity scores in the 2 study groups (Supplementary Figure 1). Further analyses could have determined whether this problem was more apparent than real. A key step in the analysis is to verify that propensity scoring was successful in properly adjusting for the confounding variables. It is agreed that the absolute standardized differences for each of the confounding (quantitative) variables should fall below 10% after adjustment. Supplementary Figure 2 indicates that this was not the case for 2 of the 6 confounding variables. Finally, propensity scoring in an observational study does not fix any hidden confounding variables. For all these reasons, the present study should be interpreted with great prudence. Nevertheless, it is an important and informative effort that should serve as an encouragement for the publication of positive or negative (no doubt a more difficult proposition) experiences, similar in scope and design, but likely to have different strengths and weaknesses,. The authors mentioned the great expectations regarding the ongoing, randomized ANCHOR (Topical or Ablative Treatment in Preventing Anal Cancer in Patients with HIV and Anal High-Grade Squamous Intraepithelial Lesions) study (ClinicalTrials.gov identifier NTC02135419). However, its aim is not to assess the screening phase per se, but the intervention it should trigger. Although randomized studies are generally the most desirable, as they minimize the risk of confounding, in their absence the results of observational studies are essential. They also tend to reflect real-world practices better.

Screening approaches to prevent cancers are usually fastidious to develop and validate and, as exemplified by the recent controversies regarding screenings for breast and prostate cancers, the cost-benefit balance can end up being strongly contested long after the strategies seem accepted [12]. We can thus better understand the many challenges to instituting a screening strategy for anal cancer in people living with HIV that parallels the strategy established for cervical cancer. Similarities have been noted, but there are discrepancies between the cervix and the anus. The latter does not have a transformation zone that may account for a lower incidence of HPV infections, but a higher incidence of cancer in the unscreened cervix, compared to the anus [13]. As noted by Revollo et al [9], screening is particularly intensive and costly for IASCC, even if patients of both sexes living with HIV represent a small fraction of the general population. Hence, looking carefully at the cost-benefit balance will be important before a strategy can be endorsed by a national public health agency. The costs will be financial and diverse, including making sure that there are adequate numbers of trained practitioners, both to screen and intervene, and developing protocols that are standardized and optimized. The costs will also be psychological, like convincing those disinclined to be screened (almost half of the subjects in the Spanish study), whatever the reason, as well as handling the impact of false-positive results. Finally, there might be physical costs. Not all the subjects treated as a result of finding high-grade anal intraepithelial neoplasia would eventually develop IASCC if left untreated. Presently, this overtreatment cannot be avoided. Fortunately, the present screening strategies for IASCC and their associated interventions do not seem to cause lasting sequellae. Nevertheless, it is useful to remember that it took 50 years to start appreciating the adverse obstetric effects of treating the cervical cancer precursors that were discovered through screening [14].

In conclusion, the Spanish study takes us a little step closer to an appropriate, validated, and cost-effective screening approach for anal cancer prevention in those living with HIV, but the remaining

ground to cover to enter public health policy could still be extensive and disputed. Ultimately, there is a very solid hope that HPV vaccination will alleviate the past challenges of prevention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. W. B. holds intellectual property in North America, Europe, Japan, and Australasia on the current commercial HPV that have been licensed by the University of Rochester to Merck and GlaxoSmithKline pharmaceutical companies, but does not receive, either directly or indirectly, any financial compensations at present and does not anticipate any in the future. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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