In our data, the median time from HIV diagnosis to cancer was 11.0 years (IQR, 4.0–18.0) for NADC and 1.5 years (0.0–8.2) for ADC. Coinfected patients developed NADC 6.0 years (3.0–8.3) later than monoinfected patients and ADC 7.1 years (3.5–10.4) later (Figure 1). The median time from HIV diagnosis to randomization in START was 1 year and, after that, the time to infection-related cancer was 0.7 (0.3–3.4) years and to infection-unrelated cancer was 2.3 (0.6–4.9) years; the maximum follow-up was 5 years. After 5 years, in our cohort, close to 40% of NADCs were diagnosed in HIV-monoinfected patients, but only just over 10% in HCV-coinfected patients. With a longer follow-up in the START trial, an increase of cancer events is expected, mainly infection unrelated; it could help to explore better the differences between both strategies, as the authors acknowledge properly in the limitations.

Our data suggest a role of HCV coinfection in cancer development, beyond hepatocellular carcinoma, as data in HIV-uninfected patients have suggested [3]. In START, the independent predictors of infection-unrelated cancer were older age and baseline CD8 count. Less than 5% of patients in START were HCV coinfected, but the prevalence was >3 times higher in patients with infection-unrelated cancer than those without cancer. Based on our data, with a longer follow-up and a prevalence of HCV coinfection close to real life, it is expected that HCV coinfection could be a predictor of infection-unrelated cancer.

The data published by Borges et al are novel and important; despite the limitations exposed, when these data are analyzed in real-life cohorts, it is likely that the gap between early and deferred ART can be even higher. More studies to understand some aspects, such as the role of CD8, are needed.

Note

Potential conflicts of interest. All authors certify. No potential conflicts of interest. The authors have 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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Reply to Meijide et al

To the Editor—We thank Meijide and colleagues [1] for their interest in our article [2]. They rightly point out that the short follow-up in the Strategic Timing of Antiretroviral Treatment (START) study [3] and an inherent low cancer risk at study entry hampered our ability to identify factors independently associated with infection-unrelated malignancies. Efforts are under way to extend follow-up beyond 2017 among START participants. This will allow us to determine with more accuracy the predictors for infection-unrelated cancer and better understand the effects of immediate vs deferred combination antiretroviral therapy initiation on cancer risk. In the meantime, data from large prospective cohort studies with long follow-up remain an invaluable source to determine risk factors for cancer among Human Immunodeficiency Virus (HIV)-infected persons.

Meijide and colleagues report the findings from an investigation involving HIV-infected persons carried out at their hospital in Spain [1]. They retrospectively classified malignancies into AIDS-defining and non-AIDS-defining cancer. An association was found between hepatitis C virus (HCV) coinfection and risk for non-AIDS-defining cancer in analyses adjusted for age, sex, and HIV transmission route. On the basis of this, they hypothesize that HCV coinfection may facilitate the development of malignancies other than hepatocellular carcinoma (HCC).

A direct comparison between Meijide et al’s results and our report is difficult owing to differences in recruitment period, study design, and categorization of malignancies. As mentioned in our report [2], we opted for classifying incident malignancies in START into infection-related and infection-unrelated cancer. Although not perfect, this classification takes into account emerging data from epidemiological surveillance [4] and establishes a framework to study the interactions between HIV, coinfection by pro-oncogenic viruses, and cancer development.

Hepatocellular carcinoma is a non-AIDS-defining cancer that may be classified as an infection-related or infection-unrelated malignancy depending on whether the patient is coinfected or not with HCV or hepatitis B virus (HBV). In START, the only HCC event was classified as an infection-unrelated cancer because it occurred in a participant without HCV or HBV coinfection. We wonder whether the increased risk of non-AIDS-defining cancer among HCV-coinfected participants in Meijide et al’s report was driven by an association with HCC. Shepherd and colleagues have recently published a report informative to this debate [5]. They investigated factors associated with infection-related and infection-unrelated cancers in EuroSIDA, a large HIV cohort with participants from across Europe, Israel, and Argentina. In analyses adjusted for demographics, HIV-specific variables, comorbidities, and smoking, there was no association between HCV coinfection
and risk for infection-unrelated cancer (adjusted hazard ratio, 0.90 [95% confidence interval, .60–1.37]; \textit{P} = .62).

\textbf{Note}

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\textbf{Definitions of Complicated Urinary Tract Infection and Pyelonephritis}

To the Editor—\textit{I have concerns regarding some of the definitions Wagenlehner et al [1] used in their trial of ceftazi- dime-avibactam vs doripenem for urinary tract infections (UTIs) because of the possible adverse impact on interpretation of trial results and on readers' understanding of how to rationally classify UTIs. First, the title and second sentence of the article indicate that pyelonephritis per se constitutes complicated UTI [1]. Although this is a common misunderstanding among nonspecialists, to specialists “complicated UTI” means UTI occurring in a host with predisposing conditions, regardless of the presenting syndrome (eg, cystitis vs pyelonephritis) or severity of illness.

Ironically, the references that Wagenlehner et al cite to support pyelonephritis as representing complicated UTI instead contradict this notion. For example, Foxman writes, “UTIs are classified as either lower (confined to the bladder) or upper (pyelonephritis), and as either uncomplicated or complicated. An uncomplicated UTI is one occurring in a normal host who has no structural or functional abnormalities, not pregnant, or who has not been instrumented (for example, with a catheter). All other UTIs are considered complicated” [2]. Johansen et al (including Dr Wagenlehner) likewise clearly distinguish between (1) clinical presentation (eg, lower vs upper UTI) and (2) risk factors for UTI, the latter being what qualify a UTI as complicated, regardless of clinical presentation [3]. Second, the study’s definition of pyelonephritis did not require fever [1]. This is curious, as most authorities include fever as a necessary criterion for pyelonephritis. Here, although 72% of subjects ostensibly had pyelonephritis, only 38% had fever. Even if all 38% were in the pyelonephritis group, this would mean that more than half of subjects with (supposed) pyelonephritis were afebrile. This either represents very mild pyelonephritis or something else entirely—for example, cystitis, plus other symptoms (nausea/vomiting or flank pain/tenderness) of a different cause.

Third, complicating factors were present in only 38% of subjects overall, including 28% without pyelonephritis and 10% with (supposed) pyelonephritis. The remaining 62% had no complicating factors, and had either mild pyelonephritis or an undefined UTI syndrome—hardly a suitable study population for a treatment trial of either complicated UTI or pyelonephritis. In view of these definitional issues, the applicability of the study’s findings to patients with true complicated UTI, or classic (febrile) pyelonephritis, is unknown.

\textbf{Note}

\textbf{Potential conflicts of interest.} J. R. J. reports personal fees from Crucell/F ganz and grants from Actavis/Forest, Merck, and Tetraphase, outside the submitted work; he also has patents pending (“High-Resolution Two-Locus Clonal Typing of Extraintestinal Pathogenic \textit{Escherichia coli},” provisional 61/749,144, and “Primers, Assays and Methods for Detecting an \textit{E. coli} subtype,” provisional 61/667,402).

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