EDITORIAL COMMENT

Vitamin E as a ‘bridge’ therapy for nonalcoholic steatohepatitis in HIV: what is waiting on the other side of the bridge?

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An increasing burden of nonalcoholic fatty liver disease (NAFLD) is observed in people living with HIV (PLWH), potentially leading to advanced liver fibrosis, cirrhosis, hepatocellular carcinoma and hepatic failure [1]. It is increasing so fast that currently nonalcoholic steatohepatitis (NASH) represents a rising indication for liver transplantation, being even more challenging in HIV [2].

NAFLD/NASH should not be seen as a liver condition only, but rather as a multisystemic disease affecting various organs, contributing to HIV-related noninfectious comorbidities (NICMs). In this perspective, NAFLD does not merely represent a risk factor, but also is involved in the pathogenesis of these age-related conditions [3], suggesting an immune-metabolic pathway in which liver plays a pivotal role. At a cellular level, Kupffer cells interact with stellate cells, in the regulation of nutrient availability and intrinsic metabolic actions, in order to maintain liver homeostasis [4]. When this equilibrium is perturbed, stellate cells induce liver fibrosis and systemic inflammatory response [5]. In this regard, HIV infection represents a unique setting where to explore liver at the crossroad between metabolism and inflammation. Bacterial translocation and dysbiosis lead to inflammation [6], whereas lipodystrophy-induced ectopic fat accumulation leads to metabolic alteration [7]. This complex interplay results in immune-metabolic disorders, including NAFLD, diabetes and, more generally, accentuated aging and early death [8].

In the setting of a weight gain epidemic affecting PLWH [9], the clinical phenotype of NAFLD in HIV resembles that observed in the general population. Importantly, this is also the case in the progressive forms of the disease with NASH and fibrosis, which are most consistently associated with features of the metabolic syndrome rather than HIV-specific factors, such as antiretroviral therapy (ART) exposure or CD4\textsuperscript{+} nadir. An alternative phenotype has also been specifically associated with either HIV or HCV infection and occasionally has been defined as ‘virus-associated fatty liver disease’ [10,11]. It is characterized by a lean constitution, associated with insulin resistance (particularly characteristic of HCV-genotype 3 infection) or central fat redistribution in HIV [10].

NAFLD complexity in HIV also stands with respect to ART-induced hepatotoxicity and significant metabolic complications exists [11]. Nevertheless, these adverse effects were mostly associated with D-drugs – didanosine and stavudine, which have been phased out in the last decade.

Particular attention should also be given to co-infected hepatitis C virus (HCV)–HIV patients previously effectively treated with direct acting antivirals (DAA) or HBV-HIV treated with tenofovir/TAF who may represent the most vulnerable patients for hepatic and extrahepatic adverse outcomes [12–14]. In this subset of patients, the question is: how much time should we wait

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before considering a new onset of immune–metabolic disturbance that is no more virus-induced? Shortly after virus suppression, an initial so-called ‘return to hepatic health’ process has been described with a reduction of fatty liver, but longer follow-up is needed to depict trajectories of steatosis and fibrosis progression. These patients may represent a nonhomogeneous group in which a strict definition of NAFLD/NASH is not applicable but still recognizes, in different proportions, the three major components of NASH: steatosis, fibrosis and inflammation, to be targeted by anti-NASH drugs.

In this intriguing scenario, Sebastiani et al. [15] in the current issue of AIDS, illustrate the first study addressing pharmacological intervention for NASH in mono-infected HIV. In this small phase 4, open-label trial, 27 HIV mono-infected patients with NASH were treated for 24 weeks with oral vitamin E 800 IU daily. Generalized linear mixed effects models showed a decrease in the three components of NASH: inflammation assessed with ALT (−27 units/l), steatosis with CAP (−22 dB/m) and hepatocyte apoptosis with cytokeratin 18 (CK-18; −123 units/l). These favorable results were statistically sustained 6 months after end of treatment, with the same magnitude of previous larger double-blind, biopsy-confirmed clinical trials in both adults and pediatric general population [16,17].

It must be stressed that the inclusion criteria of this study were based on the co-existence of fatty liver, diagnosed by controlled attenuation parameter (CAP) at least 248 dB/m, and significant hepatocyte apoptosis, defined by the serum CK-18 greater than 130.5 U/l, somehow suggesting that this noninvasive clinical diagnosis of NASH can be used in research setting also. This approach may help to recruit PLWH into adequately powered trial, but on the other side, this may limit our understanding of natural history of NASH-HIV.

In a recent article, Sebastiani and colleagues applied the same diagnostic criteria of the present study in 202 unselected mono-infected patients, identifying NASH in 11.4% of cases. Among them, 17 underwent a liver biopsy, and histology confirmed NASH in all cases, thus validating these cut-off values [18].

The results obtained by Sebastiani and colleagues are encouraging, but not really optimal. In particular, similarly to that observed in the PIVENS study [16], treatment with VitE did not improve liver fibrosis. Therefore, newer drugs addressing multiple targets of NASH are needed in the HIV setting also. At present, vitamin E treatment may be considered as a ‘bridge therapy’ only, while we wait for the availability of a new drug combination simultaneously addressing steatosis and fibrosis.

In this context, we are facing an ethical challenge. PLWH are excluded, per protocol, from any registrational trials for novel drugs for NASH, substantially limiting the therapeutically options for this most vulnerable population. The exclusion of PLWH is usually explained by regulatory agencies and pharma assuming an increased risk of drug–drug interactions (DDI) between antiretroviral therapy and novel compounds. This concern can be overcome by evaluating DDI in properly designed studies; moreover, contemporary ART, including booster-free, metabolic friendly regimens, display a substantially safer profile and less DDI. A special consideration should be given to INSTI. Regardless, all the drugs belonging to this class display a metabolic neutral effect, they have been differently associated with weight gain, representing a risk factor for NAFLD. Paradoxically, in a small study, raltegravir has been shown to reduce liver steatosis in ART switching studies [19,20]. These conflicting results may offer us the opportunity to suggest NAFLD as a biomarker of multisystemic immune-metabolic harm to be evaluated during drug development and postmarketing evaluation.

In this study, not surprisingly, lifestyle changes, offered in a dedicated counseling approach, were ineffective. Twenty-one out of 27 of participants were overweight or obese but, during the study period, no change in BMI was observed. We may assume that social–economic vulnerability or even HIV and lipodystrophy-related stigma, sometimes affecting PLWH, may have represented an additional obstacle to change sedentary or nutritional attitudes (we may trust that Sebastiani et al. [15] have introduced culturally driven Mediterranean diet suggestions to her patients living in the cold winter Quebec). This is a missed opportunity. A 7–10% reduction in body weight alone leads to NASH resolution in 64–90% of cases, fibrosis regression in 50–81% of cases and steatosis improvement in 76–100% of cases [21].

Moreover, physical activity has been proven to reduce mortality from all causes, cardiovascular disease and diabetes in patients with NAFLD [22]. It is clear that the cornerstone of lifestyle changes is patient awareness, which must be promoted in partnership and support of peer groups and patients’ organizations.

We welcome the report by Sebastiani et al. [15], as a landmark for future studies exploring an effective treatment for NASH in HIV, aiming to improve this immune–metabolic liver condition, simultaneously having the potential to reduce the burden on NICMs in PLWH.

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Conflicts of interest

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References


