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► **To cite this version:**

Eve-Isabelle Pécheur. Circulating micro-RNAs as biomarkers of liver fibrosis progression in hepatitis C virus/HIV-1-co-infected patients: a ‘miR’-velous opportunity of early diagnosis?. *AIDS. Official journal of the international AIDS Society*, 2021, 35 (9), pp.1499-1500. 10.1097/QAD.0000000000002921 . hal-03369791

HAL Id: hal-03369791

<https://hal.science/hal-03369791v1>

Submitted on 14 Oct 2021

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AIDS

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--Manuscript Draft--

Manuscript Number:	AIDS-D-21-00291
Full Title:	Circulating miRNAs as biomarkers of liver fibrosis progression in HCV/HIV-1 coinfecting patients: a « miR »-velous opportunity of early diagnosis ?
Article Type:	Editorial Comment
Keywords:	HCV-HIV-1 coinfections; miRNA; noninvasive biomarker; liver fibrosis; prediction.
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Circulating miRNAs as biomarkers of liver fibrosis progression in HCV/HIV-1 coinfecting patients : a « miR »-velous opportunity of early diagnosis ?

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The main causes of liver fibrosis are infections with the hepatitis B or C viruses (HBV and HCV, respectively), alcohol abuse, and non-alcoholic fatty liver disease. Fibrosis is a reversible exuberant wound healing and scarring process in which excessive connective tissue builds up in the organ [1], with overly abundant deposits of collagen and elastin fibrils. This dynamic phenomenon is triggered by a chronic liver injury, which causes an imbalance between excessive production (fibrogenesis) and deficient degradation (fibrolysis) of extracellular matrix (ECM), and during which several cell types are recruited onsite to help « seal off » the injury [2]. Whatever the etiology, this injury is linked to impaired hepatocyte replicative capacities and hepatocyte death. It also activates hepatic progenitor cells, triggering their proliferation and differentiation [3], which helps provide new hepatocytes and maintain the organ's functional integrity, and is accompanied by liver inflammation. In the context of virus-induced liver fibrosis, HCV coinfection with the human immunodeficiency virus 1 (HIV-1) aggravates the clinical features of the disease. Indeed, the prevalence of liver disease is 7 to 10 times greater in HIV-positive than in HIV-negative individuals, in close link with HCV coinfection [4]. Furthermore, even though HIV-1 does not infect hepatocytes but immune cells, it contributes to liver damages by fueling oxidative stress, activating the release of pro-fibrogenic cytokines such as TGF- β , and directly stimulating the production of ECM components by hepatic stellate cells. Therefore, HCV/HIV-1 coinfecting individuals are at higher risks of developing liver fibrosis and of progressing more quickly to severe liver dysfunctions.

A major pitfall in the diagnosis of liver fibrosis is that initial stages are asymptomatic, delaying the implementation of any appropriate therapy. Indeed, a successful resolution of fibrosis largely depends upon the stage and extent of scarred tissue, and treatments involve correcting the underlying condition when possible, i.e., in the case of coinfecting patients, administering appropriate antiviral therapies. Aside from liver biopsies, non-invasive strategies have been developed to evaluate the presence and extent of the liver disease, such as ultrasound imaging techniques and analyses of serum biomarkers [5]. These markers can be classified as indirect (a combination of routine liver biochemistry and general features) or direct (a reflection of liver ECM turnover and accumulation). Direct markers include soluble components of the ECM (proteolytic or inhibitory enzymes, collagen by-products, hyaluronic acid). Also algorithms combining direct and indirect biomarkers have been proposed [5].

In an attempt to identify in HCV/HIV-1 coinfecting patients serum biomarkers : (i) indicative of a liver-specific disease, and (ii) predictive of disease progression before signs of fibrosis, Martinez and coworkers focused on circulating micro-RNAs (miRNAs) (this issue,

[6]). MiRNAs are small (< 25 nucleotides) non-coding RNAs, which act as regulators of transcription by targeting messenger RNA transcripts. This results in the degradation or the inhibition of expression of these transcripts. Using miRNAs as disease biomarkers recently raised increasing interest, since these molecules are highly stable, easily detected in the circulation and some of them are organ-specific or, within a given organ, cell-type specific. In the liver, miR-122 is hepatocyte-specific, miR-192/194 are highly enriched in hepatocytes, and miR-29 is specific of hepatic stellate cells [7]. Elevated amounts in the circulation are often a *bona fide* reflection of reduced levels in the organ of origin, in link with organ dysfunction/failure.

In their study, Martinez and coworkers used large-scale deep sequencing to detect miRNAs in the plasma of 46 HCV/HIV-1 coinfecting but non fibrotic patients. These patients were followed over a 10 year-period, during which some developed liver fibrosis, others did not [6]. First, when comparing coinfecting patients with healthy individuals, a set of sixteen miRNAs was found upregulated in infected patients. Among these miRNAs, miR-122, miR-192, and miR-375 had previously been associated with liver disease [7], and miR-100, miR-99a, miR-30a, and miRNA-96-5p associated with HIV-1 infections. Second, when comparing the groups of HCV/HIV-1 coinfecting patients progressing toward liver fibrosis or not, a signature of seven miRNAs was unraveled, which strongly correlated with the progression toward liver fibrosis. These miRNAs (miR-99a, miR-100, miR-122, miR-125, miR-192, miR-194 and miR-1246) detected liver fibrosis progression with high sensitivity (88%) and specificity (85%) yields. Therefore, their plasma baseline levels could serve as a robust prediction of the advancement stage of liver fibrosis, upstream to the appearance of signs of hepatic damages.

This exploratory study still needs to be validated in larger patients cohorts, but it already opens bright perspectives to propose such a non-invasive signature for the prediction of liver disease progression in HIV-1 mono-infected patients, and in HCV/HIV-1 coinfecting patients cured of HCV infection after treatment with direct-acting antivirals. This circulating miRNA signature, or some miRNAs therein, could also be candidates to design new clinical algorithms of prediction of liver fibrosis progression in relevant patients cohorts.

Eve-Isabelle Pécheur discloses no conflict of interest.

This work was funded by the Ligue Contre le Cancer – Comité de la Loire.

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