EBioMedicine 44 (2019) 18–19

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Harnessing circulating microRNAs for early HIV diagnosis

Sandhya Vasan, Merlin L. Robb *

US Military HIV Research Program, Henry M. Jackson Foundation, Bethesda, MD, USA

Identifying and treating HIV during the initial phase of infection remains challenging. During the early phase of infection, HIV is most transmissible due to high viral load in plasma and mucosal secretions and quickly establishes a latent reservoir, which prevails over conventional approaches to cure through antiviral treatment [1].

Timely diagnosis of HIV provides multiple benefits at both individual and the population level. Initiation of ART during the initial phase of infection has been shown to preserve immune function in the blood and in mucosal tissues, such as the gut [2], a major site of the latent HIV reservoir. Early awareness of HIV status may help to reduce transmission, both by curtailing individual risk behaviors and through early administration of ART. These interventions, in turn, can help to reduce viremic load, as individuals with undetectable plasma HIV are not known to transmit the virus [3,4].

A highly sensitive and specific assay that uses a simple nucleic acid quantification method to accurately diagnose an early HIV infection, in those who show below the detection threshold of plasma HIV RNA will provide improvement in HIV diagnostics. Increasingly, the widespread use of pre-exposure prophylaxis (PrEP) has created additional diagnostic challenges, as individuals with early HIV infection who remain on continuous or intermittent PrEP have different kinetics of HIV plasma RNA levels and may have a more prolonged window of undetectability than the standard eclipse phase. Antibody-based PrEP directed against HIV envelope may remove virions from plasma but fail to prevent infection. Because HIV may remain undetectable for longer periods in the setting of PrEP, the half-life of these circulating miRNAs will need to be more closely defined and may be influenced by the percentage that is encapsulated into microvesicles or exosomes.

In an article in *EBioMedicine*, Biswas and colleagues utilize a novel approach to diagnose an early HIV infection through the identification of circulating microRNAs (miRNA) [5]. These are small non-coding RNAs present in extracellular circulation, which can reside in microvesicles, exosomes, and microparticles. By utilizing plasma samples from three independent HIV-1 infected patients collected at different stages during the early phase of infection (including three RNA+, three Ag+, and three from Ag + Ab+/seroconverted) in relation to three healthy controls, the authors analyzed 372 circulating miRNAs using PCR-array to identify a differentially expressed subset of 17 miRNAs that could serve as biomarkers for detecting early HIV-1 infection. These markers were further scrutinized to identify a panel consisting of four miRNAs, P_{eHIV-1}. Expression was quantified in 80 individuals in various stages of acute and early HIV, with either undetectable plasma HIV RNA, negative p24 antigen, or negative plasma IgG and IgM. The authors demonstrate that this plasma derived four miRNA signature panel was specific to HIV-1 infection with an impressive sensitivity of 100% and specificity of 95.8%, and that the plasma samples from HBV or HCV infected individuals had a signature similar to uninfected control samples. Other groups have similarly characterized miRNAs unique to HIV-infected individuals [6–8]. However, Biswas and colleagues are the first to apply this approach to a blinded panel of samples from 49 people with either early HIV infection or no infection to validate the predictive value. The P_{eHIV-1} miRNA panel was able to accurately identify all individuals with early HIV with 100% specificity and sensitivity, which is encouraging for its use as a diagnostic assay.

Other factors may also influence the generalizability of this assay. In this study, the gender and ethnicity of the donors were unknown. This assay would need to be further evaluated among a wide range of gender, age, and ethnic profiles. Importantly, although the subtype of HIV in these donors was unknown, there is a high likelihood they are predominantly subtype B infections, given that all donors were from sites in the USA. The applicability of these findings to non-subtype B infections, which represent most of the global HIV burden, remains to be evaluated. In addition, specificity was evaluated by comparison to a moderate number of donors with HBV and HCV infection. The high specificity of this miRNA panel to HIV is encouraging, although it should ultimately be tested in a cohort with a wide panel of viral pathogens.

Finally, despite the promise of this approach, success in the commercialization of this assay would be influenced by downstream logistic considerations. PCR-based approaches are more expensive than ELISA for diagnostics and require more specialized laboratory technology and operator expertise, thus limiting use in resource-poor settings, field settings, or at home testing. Conversely, the PCR-array approach affords high sensitivity using low blood volumes, which might allow for more widespread testing using blood from fingerstick rather than full venous phlebotomy. Similar approaches are currently being explored for other infectious viruses, such as dengue and Ebola [9,10].

In conclusion, the findings reported by Biswas and colleagues pave the way for an exciting new diagnostic path in the detection of early

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.04.023.
* Corresponding author.
E-mail address: mrobb@hivresearch.org (M.L. Robb).

https://doi.org/10.1016/j.ebiom.2019.05.017

HIV, although several questions remain before the potential for this approach can be fully harnessed.

Acknowledgment

The work was funded by a cooperative agreement from the US Department of Defense to the Henry M. Jackson Foundation for the Advancement of Military Medicine (W81XWH-07-2-0067). The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the DOD.

References

[1] Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. Aids 2003;17:1871–9.
[2] Schuetz A, Deleage C, Sereti I, Rerknimitr R, Phanuphak N, Phuang-Ngern Y, et al. Initiation of ART during early acute HIV infection preserves mucosal Th17 function and reverses HIV-related immune activation. PLoS Pathog 2014;10:e1004543.
[3] Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. The lancet HIV 2018;5:e438–47.
[4] Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. Jama 2016;316:171–81.
[5] Biswas S, Haleyurgirisetty M, Lee S, Hewlett I, Devadas K. Development and validation of plasma miRNA biomarker signature panel for the detection of early HIV-1 infection. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.04.023 S2352-3964(19)30262-2.
[6] Narla V, Bhakta N, Freedman JE, Tanriverdi K, Maka K, Deeks SG, et al. Unique circulating MicroRNA profiles in HIV infection. J Acquir Immune Defic Syndr 2018;644-650:79 *(1999)*.
[7] Thapa DR, Hussain SK, Tran WC, D'Souza G, Bream JH, Achenback CJ, et al. Serum microRNAs in HIV-infected individuals as pre-diagnosis biomarkers for AIDS-NHL. J Acquir Immune Defic Syndr 2014;229-237:66 *(1999)*.
[8] Reynoso R, Laufer N, Hackl M, Skalicky S, Monteforte R, Turk G, et al. MicroRNAs differentially present in the plasma of HIV elite controllers reduce HIV infection in vitro. Sci Rep 2014;4:5915.
[9] Duy J, Koehler JW, Honko AN, Schoepp RJ, Wauquier N, Gonzalez JP, et al. Circulating microRNA profiles of Ebola virus infection. Sci Rep 2016;6:24496.
[10] Ouyang X, Jiang X, Gu D, Zhang Y, Kong SK, Jiang C, et al. Dysregulated serum MiRNA profile and promising biomarkers in dengue-infected patients. Int J Med Sci 2016;13:195–205.