RECOMMENDED CITATION
Nunes EP, Barbosa-Lima G, Vieira YR, Cerbino-Neto J, Bozza FA, Bozza PT, et al. Insights on potential prophylactic activity of a sofosbuvir-based therapy against Zika [Submitted]. Mem Inst Oswaldo Cruz E-pub: 14 July 2017. doi: 10.1590/0074-02760170268.

Title: Insights on potential prophylactic activity of a sofosbuvir-based therapy against Zika

Running title: Sofosbuvir protection against Zika

Key-words: Zika virus, Zika, antiviral, Hepatitis C virus, Brazil, sofosbuvir

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Abstract

Sofosbuvir, clinically approved anti-hepatitis C virus (HCV) drug, inhibits Zika virus (ZIKV) replication. We wonder whether HCV-positive patients under sofosbuvir-based therapy would be less likely to have Zika. Indeed, whereas 8 of 68 untreated individuals had Zika, no case was registered among 21 individuals under this therapy.

The emergence of Zika virus (ZIKV) has been associated with congenital malformations, including microcephaly, and a broad range of neurological disorders in adults, including Guillain-Barré syndrome (1, 2). With the number of cases rising, Zika-associated deaths have also been reported (3, 4). ZIKV is an unique pathogen transmitted by mosquitos, through sexual and physical contact, and vertically (5). Therefore, antiviral interventions against ZIKV are an urgent.

ZIKV, dengue (DENV) and hepatitis C viruses (HCV) are members of the *Flaviviridae* family, sharing over 80% of sequence homology at the viral RNA polymerase level. Our group, as well as others, have demonstrated that the HCV RNA polymerase inhibitor sofosbuvir targets ZIKV replication (6-8). Considering that sofosbuvir is currently used to treat HCV-infected patients, we hypothesized that individuals undergoing treatment with sofosbuvir would be, at some level, protected against Zika.

The Instituto Nacional de Infectologia Evandro Chagas (INI) at Fiocruz, Rio de Janeiro (Rio), Brazil, provides healthcare to over 400 HCV-infected patients. Among these, 89 patients remain under active monitoring for over 2 years, with at least two medical appointments/year. From December 2015 to June 2016, 21/89 patients received sofosbuvir-based therapy, either in combination with: a) ribavirin (2 patients), b) simeprevir (3 patients), c) daclatasvir (4 patients) or d) daclatasvir/ribavirin (12

patients). The remaining 68/89 patients were treatment naïve. More importantly, this period overlaps with a massive ZIKV circulation in Rio (9). Zika diagnosis were performed according to international guidelines (10). These patients are a singular group to perform a pilot study and obtain clinical insight on the potential benefits of sofosbuvir-based therapy for prophylaxis against Zika, because they were under such treatment during the ZIKV epidemics in Rio. Institutional review board approval #42999214110015248.

The treatment-naïve patient population consisted of 72% females, average age=58 years-old (median; IQR = 51-65), 80% of the patients had HCV genotype 1 infection and 67% had hepatic injury level F3/4 (Table 1). Importantly, 8 patients were diagnosed with Zika (11.75%). This percentage is consistent with confirmed diagnosis of Zika in suspected cases, during the period of study and geographical location (9). The sofosbuvir-treated patient population consisted of 63% females, average age=57 years-old (median; IQR = 49-62); all had genotype 1 infection and 90% had level F3/4 hepatic fibrosis. Differently than the treatment-naïve population, no case of ZIKV was diagnosed among the sofosbuvir-treated individuals (Table 1).

Although retrospective serological surveillance studies to monitor anti-ZIKV IgG prevalence in these individuals would be valuable to confirm our observation, commercially available serological assays are not reliable, because it does not discriminate between anti-DENV and -ZIKV IgG. Since DENV is hyperendemic in Rio, where these patients live, retrospective serological surveillance has no clinical validity. We therefore understand that our data, although limited by the small number of patients in this pilot study, provide an insightful description of the potential clinical use of sofosbuvir against Zika. Our findings strongly suggest that individuals undergoing

treatment with sofosbuvir are likely protected against Zika, reinforcing the direct antiviral activity of this drug against ZIKV.

Acknowledgements

The authors would like to recognize the helpful contributions of Drs. Carlos M. Morel, Marcio L. Rodrigues, Renata Curi, Fabrícia Pimenta, Marcela D'alincourt-Salazar.

This work was supported by Conselho Nacional de Desenvolvimento e Pesquisa (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Funding

The funding sources had no role in the study design or analysis.

Competing Interests

Dr. Karin Brüning is a member of the BMK consortium, able to produce sofosbuvir. Otherwise, no potential conflict of interests exists.

Authors' Contributions

Conceived the study – KB, TMLS

Assisted the patients - EPN, JC-N, FAB and VGV

Analyzed the data – EPN, GB-L, YRV, VGV, TMLS

Wrote the Manuscript – EPN, VGV, TMLS

All authors approved the final version of the manuscript.

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Table 1 – Zika diagnosis, clinical and demographical data of HCV-positive patients treated with sofosbuvir-based therapies or treatment naïve

	Treatment naïve	Sofosbuvir-treated
N (individuals)	68	21
Age (years old)	58	57
IQR 25% (years old)	51	49
IQR 75% (years old)	65	62
Females (%)	72	63
HCV Genotype 1 (%)	80	100
HCV genotype 3 (%)	20	0
F3/F4 Hepatic injury (%)	67	90
Zika (n)*	8	0

*$P < 0.05$ by Logistic regression using the R-program.