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### Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome

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## CORRESPONDENCE



## Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome

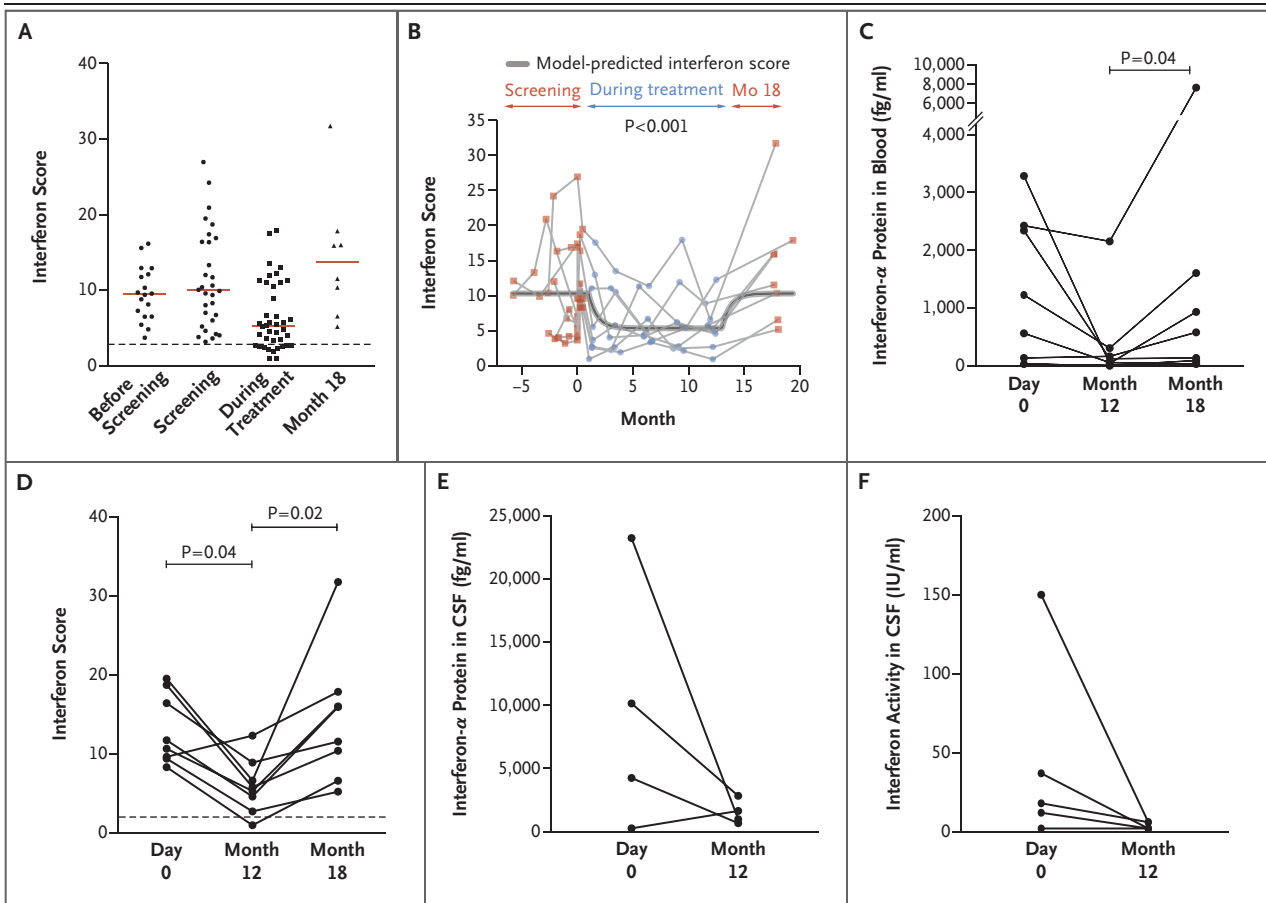
**TO THE EDITOR:** The Aicardi–Goutières syndrome is a genetic encephalopathy that is associated with childhood illness and death. The syndrome is hypothesized to be due to misidentification of self-derived nucleic acids as nonself and the subsequent induction of a type I interferon–mediated response that simulates an antiviral reaction.<sup>1</sup> Endogenous retroelements, mobile genetic elements that can be transcribed to RNA and then to DNA by reverse transcription, constitute 40% of the human genome and represent a potential source of immunostimulatory nucleic acid in patients with this syndrome.<sup>2</sup>

In a single-center, open-label, pilot study involving patients with the Aicardi–Goutières syndrome (ClinicalTrials.gov number, NCT02363452), we administered a combination of three nucleoside analogue reverse-transcriptase inhibitors — abacavir, lamivudine, and zidovudine — for 12 months, at doses used in children with human immunodeficiency virus type 1 (HIV-1) infection. The study protocol is available with the full text of this letter at NEJM.org. The primary aim was to determine the effect of treatment on the interferon score, calculated from the expression of six interferon-stimulated genes; higher scores indicate greater interferon signaling, and scores higher than 2.47 are considered to be abnormal.<sup>3</sup> Interferon status was also determined by measurement of interferon- $\alpha$  protein levels in serum, plasma, and cerebrospinal fluid (CSF); the antiviral protective capacity (interferon activity) of patient serum and CSF; and genomewide sequencing of RNA extracted from whole blood. Clinical features and cerebral blood flow (measured by means of arterial spin labeling magnetic resonance imaging) were secondary efficacy measures.

Eight of 11 patients who were recruited from a pool of 68 patients in France known to have the syndrome completed the study (Table S2 in the Supplementary Appendix, available at NEJM.org). Three patients withdrew owing to an inability to swallow the volume of the study medication. There was an effect of treatment on interferon signaling, with the median interferon score across all 8 patients falling from 9.66 (interquartile range, 6.51 to 13.23) to 5.33 (interquartile range, 2.76 to 10.90) ( $P < 0.001$ ) (Fig. 1A). Interferon- $\alpha$  protein levels in serum and plasma and interferon antiviral activity in CSF were also reduced with treatment (Table S3 in the Supplementary Appendix). This effect was greatest among the 4 patients with mutations in components of the RNase H2 complex (with the median score in these 4 patients falling from 8.16 [interquartile range, 5.41 to 11.94] to 3.51 [interquartile range, 2.49 to 5.46]). RNA sequencing indicated a reduction of global interferon-stimulated gene expression after 12 months of treatment and a return

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**Figure 1.** Measures of Interferon Status in Eight Patients Completing 12 Months of Therapy.

Panel A shows the interferon score in blood, with higher scores indicating greater interferon signaling. There were 18 recorded values before the screening period, 30 recorded values during the screening period (6 months up to and including day 0), 40 recorded values during the 12-month treatment period, and 8 recorded values at month 18 (6 months after the discontinuation of treatment). Red lines represent the median values according to time period. The dashed line indicates the mean interferon score of controls plus 2 SD; values above this line (i.e.,  $>2.47$ ) are considered to be abnormal. Panel B shows a comparison of interferon scores in blood in the 6 months before treatment, during the treatment period, and after treatment (at month 18), performed with the use of a nonlinear mixed-effects model. Panel C shows the interferon- $\alpha$  protein level in blood, Panel D the interferon score in blood, Panel E the interferon- $\alpha$  protein level in cerebrospinal fluid (CSF), and Panel F interferon activity in CSF at the indicated time points. Two patients (Patient 5 and Patient 10) did not undergo lumbar puncture. In two other patients (Patient 3 and Patient 4), an insufficient CSF sample was available at day 0, month 12, or both for assessment of the interferon- $\alpha$  protein level, interferon activity, or both. The correlation coefficient between the interferon- $\alpha$  protein level in blood and the interferon score in blood was 0.704 ( $P < 0.001$ ).

to pretreatment levels 6 months after discontinuation of therapy (Figs. S5 and S6 in the Supplementary Appendix). There was an increase in cerebral blood flow during the treatment period in 3 of 5 patients with data that could be interpreted (Fig. S8 and Table S7 in the Supplementary Appendix).

These results support the hypothesis that HIV-1 reverse-transcriptase therapy can reduce interferon signaling in patients with the Aicardi-Goutières syndrome by inhibition of reverse tran-

scription of endogenous retroelements. Changes in interferon signaling and cerebral blood flow suggest that treatment could have clinical value, perhaps in combination with other therapies (e.g., inhibitors of Janus kinase 1 and 2).<sup>4</sup> The open-label design of the study and small sample require that a larger group of patients be evaluated in a controlled clinical trial.

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