Late start of COVID treatment may still benefit immunocompromised patients

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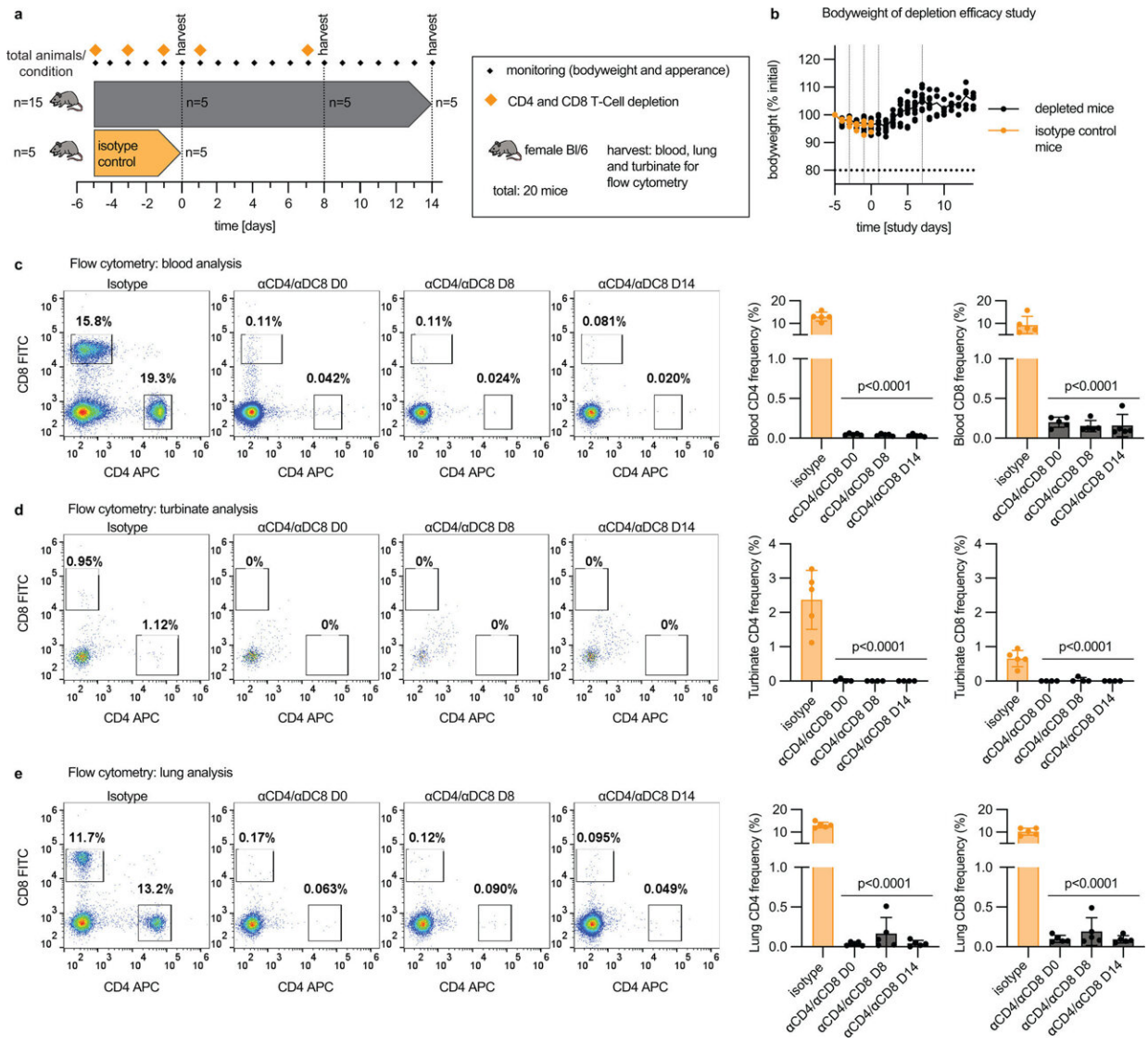

C57BL/6 CD4$^+$/CD8$^+$ T cell mouse depletion model. (a) Study schematic. Blood, turbinates, and lungs were harvested and processed for flow cytometry; n

numbers as specified. (b) Body weight curves of mice, normalized to the initial weight before the first depletion injection (study day −5). Graphs show each replicate (aligned). Horizontal dashed line denotes the predefined 20% weight-loss endpoint criteria, and vertical dashed lines indicate time of depletion injections. (c–e) Flow cytometric analysis of blood (c), turbinates (d), and lungs (e). A representative plot is shown for each analysis and condition. Right panels show CD4 and CD8 frequencies (in %). Data represent mean ± SD, *P* values based on one-way ANOVA with Dunnett post-hoc test. Credit: *Journal of Virology* (2024). DOI: 10.1128/jvi.00905-24

Starting antiviral treatment as late as 14 days after infection with SARS-CoV-2 may still be beneficial in hosts with compromised immune systems, who are at greatest risk of developing severe COVID-19, according to researchers in the Center for Translational Antiviral Research at Georgia State University's Institute for Biomedical Sciences.

While it's best to begin treatment earlier, in immunocompromised hosts, drugs like paxlovid and molnupiravir appear to inhibit replication of the virus even if they are initiated up to 14 days after infection.

The study, published in the *Journal of Virology*, offers new information about late-onset treatment introduced 14 days after infection with SARS-CoV-2, the virus that causes COVID-19. The findings demonstrate that antiviral therapeutics could have valuable clinical use in late-onset management of persistent SARS-CoV-2 infection in immunocompromised patients, in addition to reducing the risk of progression to severe disease.

The researchers sought to offer specific SARS-CoV-2 treatment plans to the immunocompromised and tested late-onset therapeutic options with standard-of-care paxlovid and molnupiravir and experimental therapeutic 4'-Fluorouridine (4'-FlU) in a T-cell depleted

immunocompromised mouse model of SARS-CoV-2.

The Centers for Disease Control and Prevention (CDC) recommends that individuals with impaired immune functions use antivirals and immunomodulatory drugs at doses and durations similar to the general patient population, but this new study indicates benefits of late treatments to mitigate persistent viral replication, the authors explained.

"Paxlovid, molnupiravir and pre-clinical candidate 4'-FlU significantly lowered virus loads in turbinates (bony structures in the nose that regulate airflow and warm and humidify air that is inhaled) when treatment was initiated 14 days after the infection for seven days," said Dr. Carolin M. Lieber, first author of the paper and a postdoctoral fellow in the Center for Translational Antiviral Research at Georgia State.

"We demonstrated that late-onset antiviral treatment can provide major therapeutic benefit to an immunocompromised host infected with SARS-CoV-2," said Dr. Richard K. Plemper, senior author of the study, Regents' Professor and Director of the Center for Translational Antiviral Research at Georgia State. "This study highlights that appropriately powered clinical trials are urgently needed to best serve the specific needs of a patient population at high risk to develop severe COVID-19."

In the study, immunocompromised mice experienced low-level viral replication for 35 days after the infection with SARS-CoV-2. When started on antivirals 14 days after infection, however, the duration of virus replication was significantly shortened, which could have implications for clinical usage of antiviral drugs in immunocompromised patients.

Additional authors of the study include Hae-Ji Kang, Vu Ngo and Andrew Gewirtz of the Institute for Biomedical Sciences at Georgia State; Elizabeth Sobolik and Alexander Greninger of the University of

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More information: Carolin M. Lieber et al, Efficacy of late-onset antiviral treatment in immunocompromised hosts with persistent SARS-CoV-2 infection, *Journal of Virology* (2024). DOI: 10.1128/jvi.00905-24