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Research Letter

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# Long-term immunogenicity and boostability of rabies pre-exposure prophylaxis (PrEP) in immunocompromised adults who received PrEP prior to the start of immunosuppressive therapy: an exploratory study

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Rabies is a zoonotic disease causing tens of thousands of deaths annually, mostly from dog bites.[1] Once symptomatic, rabies is almost always fatal, but preventable with timely post-exposure prophylaxis (PEP), comprising vaccines and rabies immunoglobulin (RIG).[1] In endemic regions, limited access to RIG and vaccines puts local populations and travellers at risk.[2] PEP for unvaccinated, immunocompetent individuals includes four vaccine doses plus RIG. Those previously vaccinated with pre-exposure prophylaxis (PrEP) need only two PEP-doses, without RIG.[1] PrEP induces immunological memory enabling rapid recall responses (boostability) for at least two decades.[1] In immunocompromised patients (ICPs) using immunosuppressive monotherapy (thiopurines or biological immunomodulators [bIM]), 90% demonstrate adequate boostability after a three-dose PrEP during immunosuppression, with 100% boostability in those with an adequate early antibody response.[3] However, data are lacking for ICPs who received PrEP before immunosuppression, in whom well-established immunological memory is expected. The World Health Organization (WHO) still recommends full PEP including RIG in these patients, even if they received PrEP.[1] As RIG is still required, its benefit is limited. Consequently, PrEP uptake amongst ICPs travelling to high-endemic areas is low (2%–9%).[4] We therefore studied a unique cohort of Dutch military personnel who received PrEP whilst still immunocompetent and later started immunosuppressive monotherapy. The aim was to assess long-term immunogenicity and boostability following a PEP booster, to determine whether RIG can be safely omitted.

This exploratory study was conducted at the Central Military Hospital in Utrecht and the Amsterdam University Medical Centres, from June to August, 2024. Dutch military guidelines changed in 2019 from a three-dose (days 0, 7, 21–28) to a two-dose (days 0,7) vaccination series; 7; with a booster after 1 year before redeployment.[5] Military personnel (18–65 years) with chronic autoimmune diseases using immunosuppressive monotherapy (thiopurines or bIM), who had received ≥two intramuscular PrEP doses ≥1 year earlier, whilst immunocompetent, received one intramuscular rabies booster vaccination (Verorab®, 1.0 mL, batch X1A662). No control group was included, as 100% boostability in immunocompetent individuals is well-established.[1] Rabies virus neutralizing antibody (RVNA) concentrations were measured at booster vaccination ($D_B0$) and

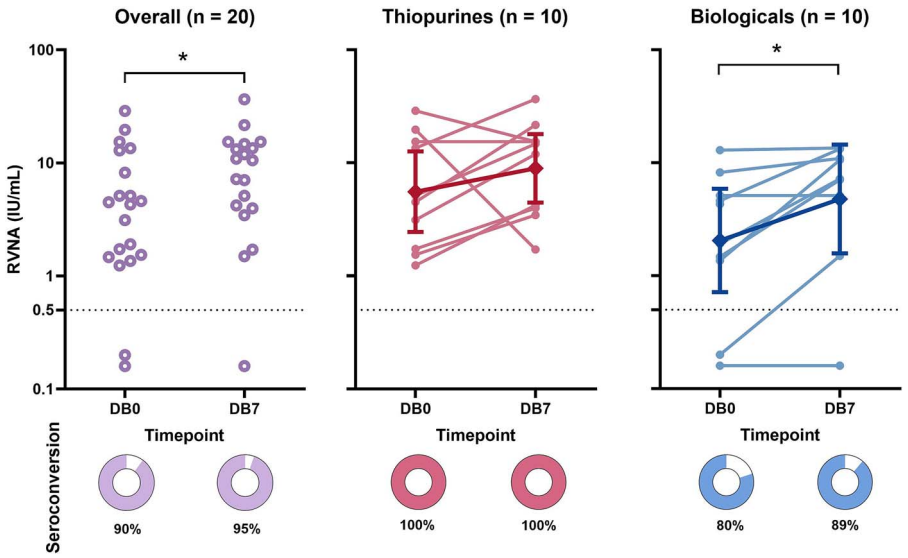


**Figure 1** Boostability in adults that started immunosuppressive therapy after rabies pre-exposure prophylaxis. The figure displays the serological responses of patients on biologicals and thiopurines who received a rabies booster vaccination 1–20 years after pre-exposure prophylaxis with at least two rabies vaccinations whilst still being immunocompetent. The diamonds depict geometric mean rabies virus neutralizing antibody (RVNA) concentrations and 95% confidence intervals. The lighter coloured lines depict RVNA concentrations of individual participants. The dotted line indicates a RVNA level of 0.5 IU/mL. The charts below display seroconversion rates (proportion of participants with RVNA levels ≥0.5 IU/mL). *Indicates a significant difference in RVNA levels.

7 days later ($D_B7$), by rapid focus fluorescent inhibition test. The primary outcome was boostability, defined as RVNA concentrations > 0.5 IU/mL at $D_B7$. Secondary outcomes were seroconversion rates (RVNA levels ≥0.5 IU/mL) at $D_B0$, geometrical mean concentrations (GMCs) on $D_B0$ and $D_B7$, and factors associated with antibody concentrations at $D_B7$. The Amsterdam UMC ethics committee (NL65687.018.18) and the Military Medical Authority (DG020231207107) approved the study. All participants provided written informed consent.

Of 20 patients included; 19 completed the study (Supplementary Figures 1 and 2). The median age was 43.5 years; 90% were male. The majority had inflammatory bowel disease. PrEP had been administered at a median 6.8 (range 1–20) years prior; 9/20 (45%) received two, and 11/20 (55%) three PrEP-doses. The median time between start immunosuppressive therapy and study booster dose was 39.5 months. 18/19 (95%) were boostable. GMCs significantly increased from 3.38 IU/mL (95%CI: 1.77–6.45) at $D_B0$ to 6.64 IU/mL (95%CI: 3.68–11.99) at $D_B7$ ($P$-value = 0.011), respectively. GMCs did not significantly differ between thiopurine and bIM users (Figure 1). A ≥ 2-fold and ≥ 4-fold increase in RVNA concentrations were observed in 42% (8/19) and 16% (3/19), respectively. The one non-responder was a 40-year-old male with Crohn's disease on adalimumab for 5 years. He had received two PrEP doses 6 months before starting immunosuppression, and exhibited no neutralization (RVNA < 0.17 IU/mL) on $D_B0$, $D_B7$, or at an additional blood sample taken 5.5 months post-booster. Regression analysis revealed no predictors of $D_B7$ antibody levels; possibly due to limited sample size (Supplementary Tables 1–3).

Our findings suggest immunological memory may persist up to 20 years after PrEP, evidenced by strong booster responses and significant GMC increases in all but one. This one individual failed to mount either a rapid or delayed booster response and had undetectable RVNA levels throughout. In a recent cohort of ICPs who received PrEP during immunosuppressive therapy, four showed no early response but all seroconverted within a month.[3] This participant's total lack of response may therefore reflect an underlying immune anomaly not solely attributable to adalimumab. To date, no studies have assessed PrEP immunogenicity in ICPs vaccinated whilst still immunocompetent.[1] Data on this population remain scarce as few receive PrEP before immunosuppression.[4] Despite extensive screening, no additional eligible participants were found. The generalisability of our findings is limited by the cohort's low comorbidity, narrow age range and male predominance (90%). Moreover, some participants received more rabies vaccinations for PrEP than advised by Dutch traveller guidelines[6] and WHO guidelines,[1] due to Dutch military protocols recommending an extra booster before redeployment.[5] Although no association was found between PrEP-dose numbers and RVNA at $D_B7$, vaccine responses may have been overestimated. Nevertheless, these data provide valuable evidence to reconsider WHO guidelines, which currently classify all ICPs as rabies-naïve, regardless of prior PrEP. In previously immunocompromised patients receiving PrEP, pre-travel antibody testing after a booster could identify those with adequate immunological recall who may not require RIG. For those immunocompetent at the time of PrEP, two approaches could be considered. A conservative approach (safety above costs) would be to adopt the same titre-based strategy as proposed for previously immunocompromised patients, given the lack of 100% boostability observed in this study. A more pragmatic approach (cost above safety) would be to regard all ICPs on immunosuppressive monotherapy who received PrEP whilst still immunocompetent, as boostable, thus precluding RIG from future PEP-regimens. Whilst this approach does not guarantee universal

protection, it aligns with current practices for immunocompetent elderly, for whom 100% boostability is also not assured.[7,8] WHO guideline changes have previously been based on comparably sized studies.[1] For example, the reclassification of HIV patients with CD4+ counts ≥200 cells/mm$^3$ as immunocompetent was supported by data from only 13 participants.[9,10] Whether the current data justify a similar revision for certain ICP subgroups remains a decision for guideline committees. Such revisions could improve rabies vaccine coverage and reduce unnecessary RIG use amongst ICPs. Finally, we recommend administrating PrEP before starting immunosuppressive therapy to enhance long-term protection in ICPs.

## Supplementary data

Supplementary data are available at *JTM* online.

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## Author contributions

Jenny Lea Schnyder (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [lead], Investigation [lead], Methodology [equal], Project administration [equal], Resources [equal], Validation [equal], Visualization [equal], Writing—original draft [lead], Conceived the study and wrote the study protocol, Responsible for participant flow and follow-up of patients, Performed data collection, Performed the statistical analyses, Wrote the First version of the manuscript), Kim van Sinderen (Methodology [supporting], Writing—original draft [supporting], Writing—review & editing [supporting], Performed the statistical analyses, Wrote the First version of the manuscript), Nita Schipper-Boer (Conceptualization [equal], Investigation [equal], Project administration [equal], Resources [equal], Software [equal], Writing—review & editing [equal], Conceived the study and wrote the study protocol, Responsible for participant flow and follow-up of patients, Performed data collection), Sanne Terryn (Resources [equal], Writing—review & editing [equal], Responsible for the laboratory analyses and supervision), Inne Nauwelaers (Resources [equal], Writing—review & editing [equal], Responsible for the laboratory analyses and supervision), Cornelis Stijnis (Project administration [equal], Resources [equal], Writing—review & editing [equal]), Martin Grobusch (Resources [equal], Supervision [equal], Writing—review & editing [equal]) and Abraham Goorhuis (Conceptualization [equal], Funding acquisition [equal], Project administration [equal], Resources [equal], Supervision [equal], Writing—original draft [equal], Writing—review & editing [equal], Conceived the study and wrote the study protocol). All authors reviewed the data, contributed to the writing of the manuscript and agreed to the final version to be submitted for publication.

**Conflict of interest:** None of the authors report competing interests.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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