

## Supplementary

**Table S1** Weighted cohort characteristics and covariate balance diagnostics before and after inverse probability of treatment weighting

| Variable                              | No antiviral therapy<br>(Before IPTW) | Acyclovir (Before<br>IPTW) | Ganciclovir (Before<br>IPTW) | SMD Before<br>IPTW | No antiviral therapy<br>(After IPTW) | Acyclovir (After<br>IPTW) | Ganciclovir (After<br>IPTW) | SMD After<br>IPTW |
|---------------------------------------|---------------------------------------|----------------------------|------------------------------|--------------------|--------------------------------------|---------------------------|-----------------------------|-------------------|
| Effective sample size                 | 371                                   | 526                        | 162                          | —                  | 365.8                                | 517.6                     | 158.4                       | —                 |
| Demographic characteristics           |                                       |                            |                              |                    |                                      |                           |                             |                   |
| Age, years                            | 4.3 (2.8–6.4)                         | 5.0 (3.5–6.8)              | 4.8 (3.3–7.1)                | 0.09               | 4.6 (3.1–6.5)                        | 4.7 (3.2–6.6)             | 4.7 (3.3–6.7)               | 0.03              |
| Male sex, n (%)                       | 208 (56.1)                            | 298 (56.7)                 | 81 (50.0)                    | 0.07               | 55.8                                 | 56.2                      | 55.6                        | 0.02              |
| Clinical severity indicators          |                                       |                            |                              |                    |                                      |                           |                             |                   |
| Fever duration before admission, days | 5.0 (3.0–7.0)                         | 6.0 (4.0–8.0)              | 6.0 (4.0–8.0)                | 0.21               | 5.8 (4.0–7.3)                        | 5.9 (4.1–7.5)             | 5.9 (4.0–7.4)               | 0.05              |
| Airway-risk indicators, n (%)         | 42 (11.3)                             | 92 (17.5)                  | 32 (19.8)                    | 0.19               | 15.4                                 | 16.2                      | 16                          | 0.05              |
| Hepatomegaly/splenomegaly, n (%)      | 86 (23.2)                             | 162 (30.8)                 | 54 (33.3)                    | 0.18               | 28.7                                 | 29.4                      | 29.9                        | 0.04              |
| Laboratory parameters                 |                                       |                            |                              |                    |                                      |                           |                             |                   |
| ALT, U/L                              | 42.4 (22.7–102.1)                     | 61.7 (29.3–129.9)          | 58.9 (28.7–143.2)            | 0.24               | 56.8 (28.1–121.0)                    | 57.6 (28.8–123.4)         | 57.1 (29.0–125.1)           | 0.05              |
| AST, U/L                              | 50.3 (38.2–76.4)                      | 60.6 (42.2–103.5)          | 64.4 (42.5–109.6)            | 0.27               | 58.9 (41.5–98.4)                     | 59.7 (42.0–99.5)          | 59.4 (42.3–100.2)           | 0.06              |
| CRP, mg/L                             | 8.4 (3.7–17.0)                        | 7.1 (3.5–14.9)             | 7.4 (3.3–14.0)               | 0.08               | 7.5 (3.4–15.2)                       | 7.6 (3.5–15.0)            | 7.4 (3.5–15.1)              | 0.03              |
| Platelet count, $\times 10^9$ /L      | 215.0 (181.0–256.0)                   | 189.0 (154.0–229.0)        | 201.0 (154.0–245.0)          | 0.22               | 198.5 (160.4–239.2)                  | 199.2 (161.0–240.1)       | 198.7 (160.8–239.8)         | 0.04              |
| Virological parameters                |                                       |                            |                              |                    |                                      |                           |                             |                   |
| EBV DNA load, $\times 10^3$ copies/mL | 303.0 (90.4–966.0)                    | 419.0 (130.0–1538.0)       | 313.0 (82.3–1395.0)          | 0.18               | 355.0 (110.0–1250.0)                 | 360.0 (115.0–1270.0)      | 358.0 (112.0–1265.0)        | 0.04              |
| Immunological parameters              |                                       |                            |                              |                    |                                      |                           |                             |                   |
| CD4+/CD8+ ratio                       | 0.27 (0.20–0.40)                      | 0.20 (0.18–0.30)           | 0.21 (0.17–0.32)             | 0.31               | 0.22 (0.18–0.33)                     | 0.22 (0.18–0.33)          | 0.21 (0.18–0.32)            | 0.06              |
| NK cells, cells/ $\mu$ L              | 80.1 (51.5–118.0)                     | 73.6 (50.7–114.1)          | 75.7 (53.4–121.7)            | 0.07               | 75.9 (51.8–116.0)                    | 76.1 (51.9–116.5)         | 75.8 (51.7–116.2)           | 0.02              |
| CD38+HLA-DR+ T cells, %               | 28.5 (20.4–39.6)                      | 34.8 (25.2–45.1)           | 35.1 (25.6–46.0)             | 0.25               | 33.1 (24.7–43.0)                     | 33.5 (25.0–43.5)          | 33.4 (25.1–43.4)            | 0.05              |

Data are presented as median (interquartile range) or weighted percentage unless otherwise indicated. Standardized mean differences (SMDs) were calculated to assess covariate balance before and after inverse probability of treatment weighting (IPTW). An SMD  $<0.10$  was considered indicative of adequate balance. Stabilized IPTW was generated using multinomial propensity scores incorporating demographic characteristics, clinical severity indicators, laboratory parameters, EBV DNA load, and immunophenotypic variables.

Table S2 Sensitivity analyses of the associations between antiviral therapy and short-term clinical outcomes

| Sensitivity analysis                               | Acyclovir vs. no antiviral, OR (95% CI) | P value | Ganciclovir vs. no antiviral, OR (95% CI) | P value |
|----------------------------------------------------|-----------------------------------------|---------|-------------------------------------------|---------|
| A. Early defervescence within 5 days               |                                         |         |                                           |         |
| Primary conventional multivariable model           | 0.34 (0.25–0.45)                        | <0.001  | 0.84 (0.56–1.25)                          | 0.39    |
| IPTW-adjusted logistic model                       | 0.38 (0.29–0.50)                        | <0.001  | 0.88 (0.61–1.28)                          | 0.50    |
| Propensity-score-matched cohort                    | 0.40 (0.29–0.55)                        | <0.001  | 0.90 (0.59–1.37)                          | 0.62    |
| Laboratory-confirmed acute EBV infection only      | 0.36 (0.26–0.49)                        | <0.001  | 0.82 (0.54–1.25)                          | 0.36    |
| Excluding potential immune impairment              | 0.35 (0.26–0.47)                        | <0.001  | 0.86 (0.57–1.30)                          | 0.47    |
| Excluding corticosteroid/immunomodulatory exposure | 0.35 (0.26–0.47)                        | <0.001  | 0.85 (0.56–1.28)                          | 0.43    |
| Antiviral initiation within 48 h                   | 0.39 (0.28–0.53)                        | <0.001  | 0.89 (0.58–1.36)                          | 0.59    |
| Excluding combined/sequential antiviral therapy    | 0.34 (0.25–0.46)                        | <0.001  | 0.83 (0.55–1.25)                          | 0.37    |
| B. Short hospital stay ≤9 days                     |                                         |         |                                           |         |
| Primary conventional multivariable model           | 0.12 (0.08–0.17)                        | <0.001  | 0.02 (0.01–0.04)                          | <0.001  |
| IPTW-adjusted logistic model                       | 0.16 (0.11–0.22)                        | <0.001  | 0.04 (0.02–0.07)                          | <0.001  |
| Propensity-score-matched cohort                    | 0.17 (0.11–0.25)                        | <0.001  | 0.05 (0.02–0.09)                          | <0.001  |
| Laboratory-confirmed acute EBV infection only      | 0.13 (0.09–0.19)                        | <0.001  | 0.03 (0.01–0.05)                          | <0.001  |
| Excluding potential immune impairment              | 0.13 (0.09–0.18)                        | <0.001  | 0.03 (0.01–0.05)                          | <0.001  |
| Excluding corticosteroid/immunomodulatory exposure | 0.12 (0.08–0.18)                        | <0.001  | 0.03 (0.01–0.05)                          | <0.001  |
| Antiviral initiation within 48 h                   | 0.16 (0.11–0.23)                        | <0.001  | 0.04 (0.02–0.08)                          | <0.001  |
| Excluding combined/sequential antiviral therapy    | 0.13 (0.09–0.18)                        | <0.001  | 0.03 (0.01–0.05)                          | <0.001  |

Odds ratios (ORs) below 1 indicate a lower probability of achieving the favorable outcome. The primary conventional models were adjusted for treatment exposure, age, EBV DNA load, CD4+/CD8+ ratio, NK-cell count, and baseline alanine aminotransferase level. IPTW estimates were obtained using stabilized multinomial propensity-score weights with truncation at the 1st and 99th percentiles. Propensity-score matching was performed using the same prespecified baseline covariates included in the propensity-score model. Sensitivity analyses were conducted by sequentially restricting or excluding patients according to the specified criteria. CI, confidence interval; EBV, Epstein-Barr virus; IPTW, inverse probability of treatment weighting; OR, odds ratio.