*Clinical Infectious Diseases*

MAJOR ARTICLE

# COVID-19 Vaccine Efficacy in Participants With Weakened Immune Systems From 4 Randomized Controlled Trials

**Amy C. Sherman,[1,a] Jessica Tuan,[2,a] Valeria D. Cantos,[3,a] Oladunni Adeyiga,[4] Scott Mahoney,[5] Ana M. Ortega-Villa,[6] Amy Tillman,[7] Jennifer Whitaker,[8] Amanda S. Woodward Davis,[9] Brett Leav,[10] Ian Hirsch,[11] Jerald Sadoff,[12] Lisa M. Dunkle,[13] Peter B. Gilbert,[9] Holly E. Janes,[9] James G. Kublin,[9] Paul A. Goepfert,[14] Karen Kotloff,[15] Nadine Rouphael,[16] Ann R. Falsey,[17] Hana M. El Sahly,[8] Magdalena E. Sobieszczyk,[18] Yunda Huang,[9] Kathleen M. Neuzil,[19] Lawrence Corey,[9,20] Beatriz Grinsztejn,[21] Glenda Gray,[22,23] Martha Nason,[6] Lindsey R. Baden,[1,b] and Cynthia L. Gay[24,b]**

[1]Department of Medicine, Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [2]Yale School of Medicine, Section of Infectious Diseases, New Haven, Connecticut, USA; [3]Division of Infectious Diseases, Emory University, Atlanta, Georgia, USA; [4]Department of Medicine, Division of Infectious Diseases, University of California, Los Angeles, Los Angeles, California, USA; [5]Department of Medicine, University of Cape Town, Desmond Tutu HIV Centre, Cape Town, South Africa; [6]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; [7]Frederick National Laboratory for Cancer Research, Clinical Monitoring Research Program Directorate, Frederick, Maryland, USA; [8]Department of Molecular Virology and Microbiology and Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; [9]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [10]Moderna Inc., Cambridge, Massachusetts, USA; [11]Vaccines & Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Cambridge, United Kingdom; [12]Janssen Vaccines and Prevention, Leiden, Netherlands; [13]Novavax, Gaithersburg, Maryland, USA; [14]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA; [15]Department of Pediatrics and the Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland, USA; [16]Hope Clinic, Emory University, Atlanta, Georgia, USA; [17]Infectious Disease Division, University of Rochester, Rochester, New York, USA; [18]Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA; [19]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland, USA; [20]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA; [21]National Institute of Infectious Diseases-Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; [22]Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [23]South African Medical Research Council, Cape Town, South Africa; and [24]Department of Medicine, Division of Infectious Diseases, UNC HIV Cure Center, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA

***Background.*** Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are highly efficacious at preventing severe disease in the general population, current data are lacking regarding vaccine efficacy (VE) for individuals with mild immunocompromising conditions.

***Methods.*** A post hoc, cross-protocol analysis of participant-level data from the blinded phase of four randomized, placebo-controlled, coronavirus disease 2019 (COVID-19) vaccine phase 3 trials (Moderna, AstraZeneca, Janssen, and Novavax) was performed. We defined a "tempered immune system" (TIS) variable via a consensus panel based on medical history and medications to determine VE against symptomatic and severe COVID-19 cases in TIS participants versus non-TIS individuals starting at 14 days after completion of the primary series through the blinded phase for each of the 4 trials. An analysis of participants living with well-controlled human immunodeficiency virus was conducted using the same methods.

***Results.*** A total of 3852/30 351 (12.7%) Moderna participants, 3088/29 868 (10.3%) Novavax participants, 3549/32 380 (11.0%) AstraZeneca participants, and 5047/43 788 (11.5%) Janssen participants were identified as having a TIS. Most TIS conditions (73.9%) were due to metabolism and nutritional disorders. Vaccination (vs placebo) significantly reduced the likelihood of symptomatic and severe COVID-19 for all participants for each trial. VE was not significantly different for TIS participants versus non-TIS for either symptomatic or severe COVID-19 for each trial, nor was VE significantly different in the symptomatic endpoint for participants with human immunodeficiency virus.

***Conclusions.*** For individuals with mildly immunocompromising conditions, there is no evidence of differences in VE against symptomatic or severe COVID-19 compared with those with non-TIS in the 4 COVID-19 vaccine randomized controlled efficacy trials.

**Keywords.** COVID-19; vaccine; HIV; immunocompromised; vaccine efficacy.

Groups who are deemed immunocompromised are composed of individuals with a variable range of immune responses to vaccines, based on the underlying illness or the type of immunosuppressive medication(s) they are prescribed. The spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine efficacy (VE) along this continuum of immune modulating conditions has not been fully characterized, especially for those with mild or intermittent immune defects.

Received 28 December 2023; editorial decision 28 March 2024; published online 10 April 2024

[a]Equal contributions for first authorship.

[b]Equal contributions for senior authorship.

Correspondence: A. C. Sherman, Brigham and Women's Hospital, Division of Infectious Diseases, 75 Francis Street, Boston, 02115 MA (acsherman@bwh.harvard.edu); J. Tuan, Yale School of Medicine, Section of Infectious Diseases, 800 Howard Ave 4th Floor, New Haven, CT 06519 (jessica.tuan@yale.edu).

**Clinical Infectious Diseases® 2024;79(2):364–74**



https://doi.org/10.1093/cid/ciae192

For individuals with severely immunocompromising illnesses such as lymphoma, solid organ transplant recipients, and stem cell transplant recipients, SARS-CoV-2 VE is poor, leading to increased risk of severe coronavirus disease 2019 (COVID-19) outcomes [1–7]. However, for individuals with conditions that represent a lesser degree of immunosuppressed state, such as autoimmune, solid tumor malignancies, and rheumatological diseases, the SARS-CoV-2 VE is less well characterized and largely influenced by the type of immune modulating therapies received [8–10]. Another subset of individuals with tempered but not severe immunodeficiency includes people with human immunodeficiency virus (HIV; PWH) with controlled HIV. Despite virological control with antiretroviral medication, there is concern for tempered immune responses and the potential for decreased VE to SARS-CoV-2 vaccines in PWH [11, 12].

In response to the COVID-19 pandemic, the COVID-19 Prevention Network (CoVPN) was formed by the National Institute of Allergy and Infectious Diseases to develop and implement phase 3 efficacy trials for novel vaccine candidates [11, 12]. These trials were harmonized to have similar protocols, timepoints of evaluation, and endpoint analyses. Overall, these vaccine clinical trials demonstrated safety and high efficacy in preventing severe COVID-19 outcomes, including hospitalization and death [13–18]. Although moderately to severely immunocompromised individuals were excluded from these phase 3 trials, the eligibility criteria were permissive of some potentially immune-modifying medical conditions and treatments, including PWH with adequate virologic control.

Discerning subtleties in immune dysfunction and dysregulation is a highly nuanced process; as a result, different criteria were used to define immunocompromising medical conditions and medications in these trials [19, 20]. Because none of the studies' objectives included the evaluation of VE among mildly immunocompromised individuals, the eligibility criteria differed slightly across the 4 trials, with some trials being more permissive than others of including individuals with potentially immunocompromising conditions and/or taking immunomodulating medications. To create a standardized definition that accounted for these subtleties, we reviewed all baseline medical conditions and medications to identify those that may impact the immune system across 4 CoVPN-organized SARS-CoV-2 vaccine clinical trials: COVE (Moderna/mRNA-1273) [13, 14], AZD1222 (AstraZeneca/AZD1222) [16, 21], ENSEMBLE (Janssen/AD26.COV2.S) [17, 18], and PREVENT-19 (Novavax/NVX-CoV2373) [15], henceforth referred to as Moderna, AstraZeneca, Janssen, and Novavax, respectively. We then categorized clinical trial participants as either having tempered immune systems (TIS) or non-TIS (NTIS) at baseline based on the consensus definition. The objective of this study was to determine the VE of each COVID-19 vaccine candidate among participants with TIS compared with those with NTIS.

## METHODS

### Study Design and Setting

We conducted a post hoc, cross-protocol analysis of participant-level data from the blinded phase of 4 randomized, placebo-controlled, COVID-19 vaccine phase 3 trials: Moderna (NCT04470427), AstraZeneca (NCT04516746), Janssen (NCT04505722), and Novavax (NCT04611802). The TIS derivation analysis included participants who were randomized to either the vaccine or placebo and received at least the first study injection (full analysis set). Efficacy analyses were restricted to the full analysis set (including baseline SARS-CoV-2–positive participants) and per-protocol analysis set (consistent with the primary analysis of each trial: participants received all planned injections without any major protocol violations, baseline SARS-CoV-2–positive participants were excluded) [13–18]. Participants in both sets are presented according to the actual received treatment (vaccine or placebo). Data accrued through the completion of the blinded phases of the trials were analyzed. Full details of the individual study protocols and primary efficacy analyses have been published and a comparison table of the clinical trial protocol eligibility criteria for the immunocompromised cohort was created (Supplementary Table 1). The trial time periods through unblinding/crossover and countries in which they were conducted have been summarized previously [12, 22].

### Defining the TIS Variable

To define the TIS variable, baseline medical history data and medication data were reviewed for participants in the full analysis set (see full list of terms and medications in the Supplementary Methods). This was done blinded to treatment group and outcomes. Solicited comorbidity questionnaire data after enrollment were not considered. Individuals with moderate to severe immunocompromising conditions were not included because these individuals were excluded by the parent studies' eligibility criteria. Medical Dictionary for Regulatory Activities (MedDRA, versions 23.0, 23.1, and 24.0) and World Health Organization (WHO) Drug Dictionary (DD, March 2020 and 2021) were used across the 4 trials; the medical diagnosis listed in the medical history electronic case report form of each participant was available and coded using MedDRA, and medications listed in the electronic case report form of each participant were available and coded using the WHO DD. For general medical history, the following MedDRA terms were considered: system organ class, high-level group term, high-level term, and preferred term. For medications, WHO DD Anatomical Therapeutic Chemical first- and second-level terms and standardized medication names were considered, and in some cases, route of medication was required.

Six physician reviewers, blinded to treatment status and outcomes, independently scored higher-level terms as "all,"

"some," or "none" for inclusion in the TIS definition. If there were discordant results for a given term, the term was discussed with the other reviewers to reach a consensus agreement. If "all" or "none" was selected after consensus was reached, all lower-level terms for the given higher-level term were included in the TIS definition for "all" or excluded for "none." If "some" was selected, an additional review cycle was required, and the reviewers would independently review the respective lower-level terms until all terms were scored and a consensus was reached on TIS inclusion (yes/no). All reviewers scored the terms independently and were blinded to study outcomes and treatment assignment (placebo or vaccine). The process of identifying a participant to be part of the "TIS" group or not was the same for all vaccine platforms. Also, participants could only be considered "TIS" once, by medical history or medication. Refer to Supplementary Table 2 for details about the TIS derivation and data review process.

After the first complete data review, the 6 reviewers defined time windows of interest relative to the first injection of study product. For the iterative data reviews, windowing was applied first. For baseline medical history data, terms were considered for review if related to HIV or if the medical history event was 2 years before the first injection of study product [23]. The medical conditions included, but were not limited to, history of malignancy (eg, solid tumor), end-stage renal disease, advanced liver disease, HIV, and certain autoimmune conditions. In situ or localized malignancies (eg, localized breast cancer) and localized skin cancers were not included in the immunocompromising medical conditions definition. We also analyzed the subpopulation of PWH compared with those without HIV. Immunocompromising medications were considered for review if taken 1 year before the first injection of study product [24] and included but were not limited to systemic steroids (topical and inhaled steroids were excluded from the immunocompromising medications definition), biologics, and antineoplastic agents.

### Study Outcomes

The primary study outcome was time to symptomatic COVID-19 as a function of both vaccination and TIS versus NTIS. Cases were counted starting at 14 days after completion of the primary series through the initial blinded phase for each of the 4 trials. Symptomatic COVID-19 was defined across the 4 trials as a positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction test and systemic and/or respiratory symptoms [12]. These outcomes are used to examine both the VE among those with and without TIS and the effect of TIS among those who received vaccine or placebo. The secondary study outcomes included: (1) a similar examination of the effects of vaccination and TIS status against severe COVID-19 and (2) the effects of vaccination and diagnosed with HIV on time to symptomatic COVID-19. Of note, criteria for defining severe COVID-19 included shortness of breath at rest or respiratory distress, respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of peripheral oxygen ≤93% on room air, respiratory or multiorgan failure, intensive care unit admission, or death.

### Statistical Analyses

Demographic and baseline characteristics were analyzed for each trial and were summarized with descriptive statistics. The symptomatic COVID-19 and severe COVID-19 endpoints were evaluated with the full analysis cohort of participants who received at least the first injection of study product. The COVID-19 endpoints were also evaluated in the per-protocol analysis set, consisting of participants who received all planned injections without any major protocol violations and were seronegative at baseline, as defined in each trial. Time after vaccination until event was modeled using Cox proportional hazard regression models with interactions between vaccination, study, and either the TIS/NTIS variable or the PWH variable. These models were adjusted for age (continuous), sex (defined as female/non-female), race (White; American Indian or

**Table 1. Population Summary**

| | Moderna | AstraZeneca | Janssen | Novavax | Total |
|---|---|---|---|---|---|
| Full analysis population (N) | 30 351 | 32 380 | 43 788 | 29 868 | 136 388 |
| NTIS | 26 499 (87%) | 28 831 (89%) | 38 741 (88%) | 26 780 (90%) | 120 852 (89%) |
| TIS | 3852 (13%) | 3549 (11%) | 5047 (12%) | 3088 (10%) | 15 536 (11%) |
| Persons with HIV | 180 (0.6%) | 547 (1.7%) | 1198 (3%) | 246 (0.8%) | 2171 (2%) |
| Medication of interest within 1 y of first injection | 252 (0.8%) | 245 (0.7%) | 161 (0.4%) | 156 (0.5%) | 814 (0.6%) |
| Per-protocol population | 28 451 | 26 141 | 39 185 | 25 657 | 119 434 |
| NTIS | 24 822 (87%) | 23 326 (89%) | 34 851 (89%) | 23 055 (90%) | 106 054 (89%) |
| TIS | 3629 (13%) | 2815 (11%) | 4334 (11%) | 2602 (10%) | 13 380 (11%) |
| Persons with HIV | 162 (0.6%) | 428 (2%) | 944 (2%) | 198 (0.8%) | 1732 (2%) |
| Medication of interest within 1 y of first injection | 226 (0.8%) | 186 (0.7%) | 102 (0.3%) | 125 (0.5%) | 639 (0.5%) |

Full analysis population includes participants who received at least the first study injection (placebo or vaccine); 1 AstraZeneca participant enrolled at 2 different sites and was excluded. Per-protocol population includes participants who received all planned injections without any major protocol violations and were SARS-CoV-2–negative at baseline.

Abbreviations: NTIS, non-TIS; TIS, tempered immune system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2. Demographic and Clinical Characteristics of Participants, Full Analysis Population**

| | Moderna | | AstraZeneca | | Janssen | | Novavax | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | TIS (3852) | NTIS (26,499) | TIS (3549) | NTIS (28,831) | TIS (5047) | NTIS (38,741) | TIS (3088) | NTIS (26,780) |
| Full analysis population (%) | | | | | | | | |
| Placebo | 1929 (50.1) | 13 237 (50.0) | 1236 (34.8) | 9557 (33.1) | 2526 (50.0) | 19 364 (50.0) | 1051 (34.0) | 8889 (33.2) |
| Vaccine | 1923 (49.9) | 13 262 (50.0) | 2313 (65.2) | 19 274 (66.9) | 2521 (50.0) | 19 377 (50.0) | 2037 (66.0) | 17 891 (66.8) |
| Age, y (%) | | | | | | | | |
| <65 | 2274 (59.0) | 20 556 (77.6) | 2175 (61.3) | 22 893 (79.4) | 3408 (67.5) | 31 820 (82.1) | 2271 (73.5) | 23 843 (89.0) |
| ≥65 | 1578 (41.0) | 5943 (22.4) | 1374 (38.7) | 5938 (20.6) | 1639 (32.5) | 6921 (17.9) | 817 (26.5) | 2937 (11.0) |
| Sex (%) | | | | | | | | |
| Female | 1478 (38.4) | 12 895 (48.7) | 1098 (30.9) | 13 268 (46.0) | 2026 (40.1) | 17 709 (45.7) | 1231 (39.9) | 13 110 (49.0) |
| Male | 2374 (61.6) | 13 604 (51.3) | 2451 (69.1) | 15 563 (54.0) | 3020 (59.8) | 21 026 (54.3) | 1857 (60.1) | 13 670 (51.0) |
| Intersex | … | … | … | … | 1 (<1) | 5 (<1) | … | … |
| Unknown | 45 (1.2) | 243 (0.9) | … | … | 0 (0.0) | 1 (<1) | … | … |
| Country (%) | | | | | | | | |
| Argentina | … | … | … | … | 359 (7.1) | 2637 (6.8) | … | … |
| Brazil | … | … | … | … | 788 (15.6) | 6491 (16.8) | … | … |
| Chile | … | … | 107 (3.0) | 2092 (7.3) | 121 (2.4) | 1012 (2.6) | … | … |
| Columbia | … | … | … | … | 220 (4.4) | 4028 (10.4) | … | … |
| Mexico | … | … | … | … | 121 (2.4) | 358 (0.9) | 130 (4.2) | 1634 (6.1) |
| Peru | … | … | 91 (2.6) | 1372 (4.8) | 153 (3.0) | 1618 (4.2) | … | … |
| South Africa | … | … | … | … | 1151 (22.8) | 5425 (14.0) | … | … |
| United States | 3852 (100.0) | 26 499 (100.0) | 3351 (94.4) | 25 367 (88.0) | 2134 (42.3) | 17 172 (44.3) | 2958 (95.8) | 25 146 (93.9) |
| Ethnicity (%) | | | | | | | | |
| Hispanic or Latino | 802 (20.8) | 5431 (20.5) | 701 (19.8) | 6521 (22.6) | 2001 (39.6) | 17 838 (46.0) | 628 (20.3) | 5922 (22.1) |
| Not Hispanic or Latino | 3017 (78.3) | 20 823 (78.6) | 2796 (78.8) | 21 881 (75.9) | 2887 (57.2) | 19 956 (51.5) | 2448 (79.3) | 20 791 (77.6) |
| Unknown | 33 (0.9) | 245 (0.9) | 52 (1.5) | 429 (1.5) | 159 (3.2) | 947 (2.4) | 12 (0.4) | 67 (0.3) |
| Race (%) | | | | | | | | |
| American Indian or Alaska Native[a] | 30 (0.8) | 204 (0.8) | 87 (2.5) | 1194 (4.1) | 277 (5.5) | 3866 (10.0) | 172 (5.6) | 1800 (6.7) |
| Asian | 133 (3.5) | 1262 (4.8) | 130 (3.7) | 1299 (4.5) | 134 (2.7) | 1295 (3.3) | 98 (3.2) | 1136 (4.2) |
| Black or African American | 546 (14.2) | 2553 (9.6) | 559 (15.8) | 2126 (7.4) | 1466 (29.0) | 7049 (18.2) | 587 (19.0) | 2932 (10.9) |
| Native Hawaiian or Other Pacific Islander | 10 (0.3) | 58 (0.2) | 24 (0.7) | 57 (0.2) | 20 (0.4) | 83 (0.2) | 10 (0.3) | 60 (0.2) |
| White | 2943 (76.4) | 21 093 (79.6) | 2589 (73.0) | 22 997 (79.8) | 2727 (54.0) | 22 974 (59.3) | 2156 (69.8) | 20 259 (75.6) |
| Multiple races | 70 (1.8) | 568 (2.1) | 75 (2.1) | 693 (2.4) | 269 (5.3) | 2186 (5.6) | 42 (1.4) | 442 (1.7) |
| Unknown/Other | 120 (3.1) | 761 (2.9) | 85 (2.4) | 466 (1.6) | 154 (3.1) | 1288 (3.3) | 23 (0.7) | 151 (0.6) |
| Baseline SARS-CoV-2 serostatus | | | | | | | | |
| Negative (%) | 3786 (98.3) | 25 878 (97.7) | 3443 (97.0) | 28 000 (97.1) | 4393 (87.0) | 34 934 (90.2) | 2874 (93.1) | 25 014 (93.4) |
| Positive (%) | 66 (1.7) | 621 (2.3) | 106 (3.0) | 831 (2.9) | 654 (13.0) | 3807 (9.8) | 214 (6.9) | 1766 (6.6) |
| HIV medical history | | | | | | | | |
| No | 3672 (95.3) | 26 499 (100.0) | 3002 (84.6) | 28 831 (100.0) | 3849 (76.3) | 38 741 (100.0) | 2842 (92.0) | 26 780 (100.0) |
| Yes | 180 (4.7) | 0 (0.0) | 547 (15.4) | 0 (0.0) | 1198 (23.7) | 0 (0.0) | 246 (8.0) | 0 (0.0) |

Full analysis population includes participants who received at least the first study injection (placebo or vaccine) and are presented according to the treatment they received; one AstraZeneca participant enrolled at two different sites and was excluded.

Abbreviations: NTIS, non-TIS; TIS, tempered immune system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Category is defined across all clinical sites. Indigenous people from South America were classified together with the American Indian or Alaska Native United States and Mexico demographic according to the US Food and Drug Administration definition (American Indian or Alaska Native: a person having origins in any of the original peoples of North and South America [including Central America], and who maintains tribal affiliation or community attachment). In this analysis, the Moderna, AstraZeneca, Janssen, and Novavax trials included 234, 298, 226, and 1972 participants, respectively, who identified as American Indian or Alaskan Native from North America.

Alaska Native; a combined Asian, Native Hawaiian, and Other Pacific Islander category; Black or African American; Multiple Races; Unknown Race; and Other), and baseline SARS-CoV-2 status (full analysis cohort only). Vaccine efficacy is defined as 1 – hazard ratio from the Cox models. Follow-up times were censored if the participant withdrew or was lost to follow-up, received a COVID-19 vaccine outside of the study, or reached the end of the blinded follow-up. Tests of categorical variables in the Cox proportional hazards models were performed via F tests. Demographics are summarized by N (%) for categorical variables and median (interquartile range) for continuous variables. All statistical analyses were performed using R statistical software (version 4.3.0, R Foundation for Statistical Computing) [25].

**Table 3. Summary of Most Common Conditions and Medications for the TIS Population**

| | Moderna | AstraZeneca | Janssen | Novavax | Total |
|---|---|---|---|---|---|
| Full analysis population, N | 30 351 | 32 380 | 43 788 | 29 868 | 136 387 |
| TIS population, N (% of total) | 3852 (12.7) | 3549 (11) | 5047 (11.5) | 3088 (10.3) | 15 536 (11.4) |
| Conditions/medications[a], N (% of TIS) | | | | | |
| Medication of interest 1 y prior | 252 (6.5) | 245 (6.9) | 161 (3.2) | 156 (5.1) | 814 (5.2) |
| MH HIV event or MH event of interest 2 y prior | 3649 (94.7) | 3332 (93.9) | 4915 (97.4) | 2965 (96) | 14861 (95.7) |
| MH HIV event | 180 (4.7) | 547 (15.4) | 1198 (23.7) | 246 (8) | 2171 (14) |
| Metabolism and nutrition disorders | 3029 (78.6) | 2554 (72) | 3384 (67) | 2515 (81.4) | 11 482 (73.9) |
| Type 2 diabetes mellitus | 2569 (66.7) | 2357 (66.4) | 3190 (63.2) | 2349 (76.1) | 10 465 (67.4) |
| Type 1 diabetes mellitus | 186 (4.8) | 188 (5.3) | 160 (3.2) | 164 (5.3) | 698 (4.5) |
| Diabetes mellitus | 269 (7) | 9 (0.3) | 27 (0.5) | 1 (<0.1) | 306 (2) |
| Infections and infestations | 165 (4.3) | 525 (14.8) | 1161 (23) | 227 (7.4) | 2078 (13.4) |
| HIV infection | 162 (4.2) | 510 (14.4) | 1142 (22.6) | 226 (7.3) | 2040 (13.1) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 507 (13.2) | 314 (8.8) | 419 (8.3) | 217 (7) | 1457 (9.4) |
| Prostate cancer | 122 (3.2) | 93 (2.6) | 109 (2.2) | 41 (1.3) | 365 (2.3) |
| Breast cancer | 74 (1.9) | 29 (0.8) | 57 (1.1) | 29 (0.9) | 189 (1.2) |
| Squamous cell carcinoma | 53 (1.4) | 41 (1.2) | 27 (0.5) | 34 (1.1) | 155 (1) |
| Malignant melanoma | 50 (1.3) | 30 (0.8) | 32 (0.6) | 19 (0.6) | 131 (0.8) |
| Corticosteroids for systemic use | 153 (4) | 73 (2.1) | 88 (1.7) | 78 (2.5) | 392 (2.5) |
| Prednisone | 74 (1.9) | 37 (1) | 45 (0.9) | 39 (1.3) | 195 (1.3) |
| Immunosuppressants | 77 (2) | 150 (4.2) | 65 (1.3) | 67 (2.2) | 359 (2.3) |
| Immunotherapy | 12 (0.3) | 90 (2.5) | 5 (0.1) | 3 (0.1) | 110 (0.7) |
| Hydroxychloroquine | 27 (0.7) | 32 (0.9) | 19 (0.4) | 12 (0.4) | 90 (0.6) |
| Investigations | 17 (0.4) | 23 (0.6) | 44 (0.9) | 21 (0.7) | 105 (0.7) |
| HIV test positive | 15 (0.4) | 22 (0.6) | 44 (0.9) | 18 (0.6) | 99 (0.6) |
| Musculoskeletal and connective tissue disorders | 21 (0.5) | 16 (0.5) | 19 (0.4) | 22 (0.7) | 78 (0.5) |
| Systemic lupus erythematosus | 21 (0.5) | 16 (0.5) | 19 (0.4) | 22 (0.7) | 78 (0.5) |
| Antineoplastic agents | 25 (0.6) | 21 (0.6) | 14 (0.3) | 15 (0.5) | 75 (0.5) |

MH events and medications are coded according to MedDRA and WHO DD, respectively, and counts in each row are unique participants.

Abbreviations: ATC, anatomical therapeutic chemical; DD, Drug Dictionary; MedDRA, Medical Dictionary for Regulatory Activities; MH, medical history; PT, preferred term; SOC, system organ class; TIS, tempered immune system; WHO, World Health Organization.

[a]Conditions/medications (MedDRA system organ class/preferred terms (SOC/PT) or WHO defined daily dose/anatomic therapeutic chemical (DDD/ATC) level 2/standardized medication) with total percentage ≥0.5% are included in the table.

## RESULTS

### Application of the TIS Definition

A full list of reviewed and included terms from the medical history and reported medications is provided in Supplementary Materials. The consensus definition was subsequently applied to the 4 clinical trials (Table 1) with the baseline demographics and characteristics of the participants in the full analysis cohort described in Table 2 and the per-protocol analysis described in Supplementary Table 3. The TIS group is balanced between the 2 treatment groups, as expected per randomization procedures. For the Moderna, Novavax, AstraZeneca, and Janssen trials, 3852/30 351 (12.7%), 3088/29 868 (10.3%), 3549/32 380 (11.0%), and 5047/43 788 (11.5%), met the definition of TIS in the full analysis set, respectively.

### Baseline Demographic Results

For the Moderna trial, participants with TIS had higher representation of people assigned male at birth (61.6% vs 51.3%), Black race (14.2% vs 9.6%), and aged 65 years or older (41% vs 22.4%) compared with the NTIS group. For the Novavax trial, those with TIS had higher representation of people assigned male at birth (60.1% vs 51%), Black race (19% vs 10.9%), and aged 65 years or older (26.5% vs 11%). For the AstraZeneca trial, participants with TIS had higher representation of people assigned male at birth (69.1% vs 54%), Black race (15.8% vs 7.4%), were aged 65 years or older (38.7% vs 20.6%), and US enrollees (94.4% vs 88%). For the Janssen trial, participants with TIS had higher representation of people assigned male at birth (59.8% vs 54.3%), people of Black race (29% vs 18.2%), who were aged 65 years or older (32.5% vs 17.9%), and South African enrollees (22.8% vs 14%) compared with the NTIS group.

### Clinical Characteristics at Enrollment

The subset of participants with TIS and a diagnosis of HIV was determined for each trial according to HIV medical history terms identified by the 6 reviewers. Of note, all participants with HIV met eligibility criteria for enrollment per the specific trial and thus had well-controlled HIV on antiretroviral medications, by self-report (see Supplementary Table 1 for HIV viral load and CD4 criteria per each trial's protocol). For the Moderna, Novavax, AstraZeneca, and Janssen trials, 180/3852 (4.7%), 246/3088 (8.0%), 547/3549 (15.4%), and 1198/5047

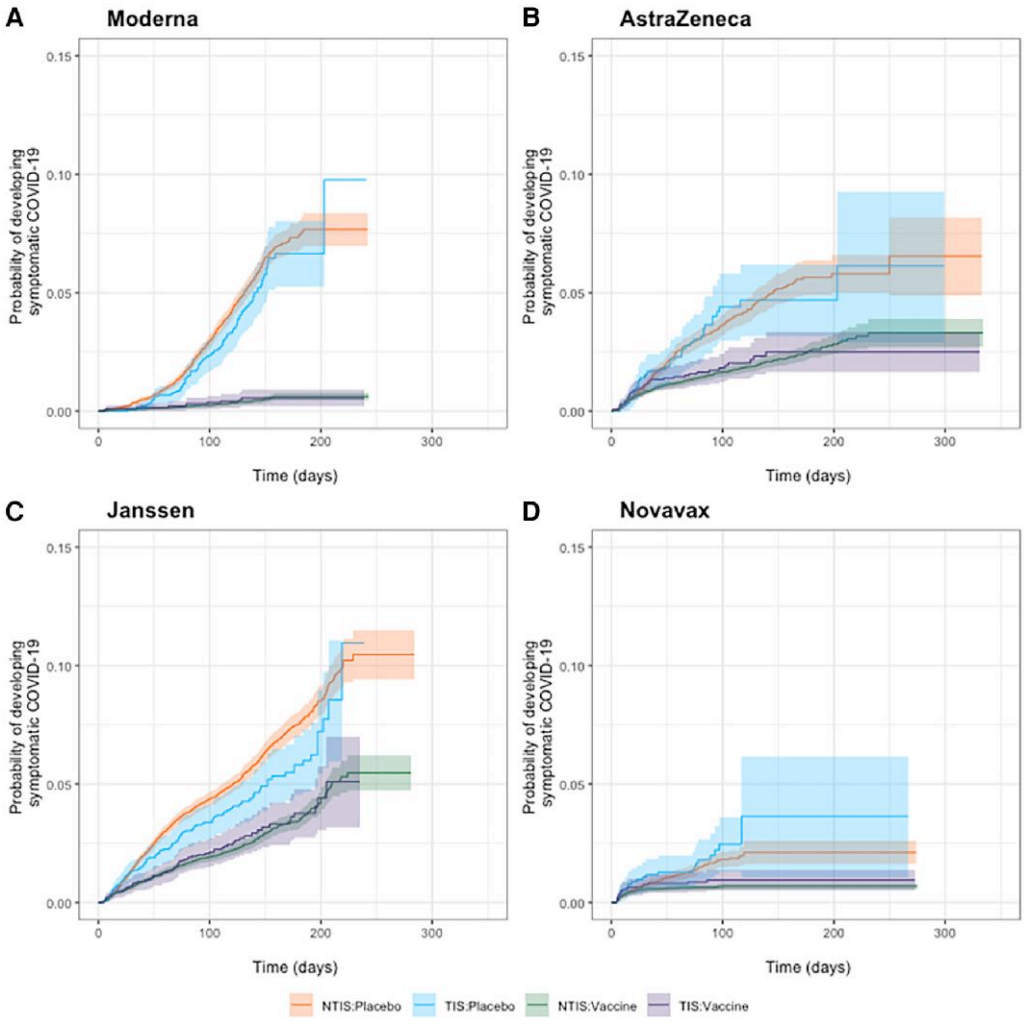


**Figure 1.** Probability of developing symptomatic coronavirus disease 2019 (COVID-19), full analysis set. Individuals with tempered immune systems (TIS) are plotted with non-TIS (NTIS) individuals who received placebo or vaccine through the blinded phase for each of the 4 trials: Moderna (*A*), AstraZeneca (*B*), Janssen (*C*), and Novavax (*D*).

(23.7%) individuals within the TIS group were identified as PWH, respectively. Other common medical conditions that met the TIS definition included metabolism and nutrition disorders (73.9% of TIS participants) and solid neoplasms (9.4% of TIS participants). Common medications that met the TIS definition included systemic low-dose corticosteroids (2.5% of the TIS participants) and immunosuppressants (2.3% of the TIS participants) and antineoplastic medications (eg, methotrexate, fluorouracil; 0.5% of the TIS participants). Conditions or medications with ≥ 0.5% are summarized in Table 3, with all terms listed in Supplementary Table 4.

Among participants identified with TIS in the Moderna, Novavax, AstraZeneca, and Janssen trials, 66/3852 (1.7%), 214/3088 (6.9%), 106/3549 (3%), and 654/5047 (13%) were positive for SARS-CoV-2 (polymerase chain reaction) at baseline, respectively.

### Vaccine Efficacy Against Symptomatic and Severe COVID-19: Individuals With TIS

We compared VE against COVID-19 between the TIS and NTIS participants with the placebo and vaccine groups represented through the blinded phase in Figure 1, with total case counts by study and TIS versus NTIS reported in Table 4. We then assessed VE among those with and without TIS, separately, as well as the effect of having TIS (compared with those without TIS, as summarized by the hazard ratio) among those who received placebo or vaccine, by study. For the full analysis set, there was no statistically significant evidence of an interaction between vaccination and TIS status for either symptomatic COVID-19 ($P = .094$) or severe COVID-19 ($P = .306$); (Figure 2 and Supplementary Table 5), suggesting that VE does not differ between TIS and NTIS participants. However, among placebo recipients, there was an overall increased

**Table 4. COVID-19 Cases by Study in TIS and NTIS Participants**

| | Moderna | | | | AstraZeneca | | | | Janssen | | | | Novavax | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TIS (N = 3852) | | NTIS (N = 26 499) | | TIS (N = 3549) | | NTIS (N = 28 831) | | TIS (N = 5047) | | NTIS (N = 38 741) | | TIS (N = 3088) | | NTIS (N = 26 780) | |
| | Vaccine | Placebo | Vaccine | Placebo | Vaccine | Placebo | Vaccine | Placebo | Vaccine | Placebo | Vaccine | Placebo | Vaccine | Placebo | Vaccine | Placebo |
| Full analysis population, N (%) | 1923 (49.9) | 1929 (50.1) | 13 262 (50.0) | 13 237 (50.0) | 2313 (65.2) | 1236 (34.8) | 19 274 (66.9) | 9557 (33.1) | 2521 (50.0) | 2526 (50.0) | 19 377 (50.0) | 19 364 (50.0) | 2037 (66.0) | 1051 (34.0) | 17 891 (66.8) | 8889 (33.2) |
| Symptomatic | 10 (0.5) | 98 (5.1) | 63 (0.5) | 744 (5.6) | 68 (2.9) | 110 (8.9) | 332 (1.7) | 328 (3.4) | 68 (2.7) | 110 (4.4) | 517 (2.7) | 1081 (5.6) | 18 (0.1) | 21 (2.0) | 115 (0.6) | 135 (1.5) |
| Severe | 1 (0.05) | 26 (1.3) | 3 (0.02) | 89 (0.7) | 1 (0.04) | 6 (0.5) | 5 (0.03) | 12 (0.1) | 16 (0.6) | 36 (1.4) | 49 (0.3) | 193 (1.0) | 1 (0.05) | 2 (0.2) | 5 (0.03) | 3 (0.03) |
| Per-protocol population, N (%) | 1827 (50.3) | 1802 (49.7) | 12 460 (50.2) | 12 362 (49.8) | 1847 (65.6) | 968 (34.4) | 15 770 (67.6) | 7553 (32.4) | 2156 (49.7) | 2178 (50.3) | 17 421 (50.0) | 17 430 (50.0) | 1720 (66.1) | 882 (33.9) | 15 552 (67.5) | 7503 (32.5) |
| Symptomatic | 5 (0.3) | 93 (5.2) | 51 (0.4) | 676 (5.5) | 10 (0.5) | 22 (2.3) | 131 (0.8) | 162 (2.1) | 67 (3.1) | 103 (4.7) | 510 (2.9) | 1067 (6.1) | 3 (0.2) | 10 (1.1) | 18 (0.1) | 79 (1.1) |

Full analysis population includes participants who received at least the first study injection (placebo or vaccine); 1 AstraZeneca participant enrolled at 2 different sites and was excluded. Per-protocol population includes participants who received all planned injections without any major protocol violations and were SARS-CoV-2 negative at baseline.

Abbreviations: NTIS, non-TIS; TIS, tempered immune system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

hazard of symptomatic and severe COVID-19 between TIS and NTIS ($P = .001$ and $P < .001$, respectively; Supplementary Table 5); this effect did not depend on which study the participant was enrolled in.

For the per-protocol analysis set, only the symptomatic COVID-19 endpoint was analyzed because few severe COVID-19 outcomes occurred among participants who received the vaccines. We again found that there were no significant interactions observed between TIS and vaccination (symptomatic $P = .249$), suggesting that there is no evidence that VE is different between the TIS and NTIS participants for each trial (Supplementary Table 6). As observed in the full analysis set, TIS did significantly increase the hazard of symptomatic COVID-19 ($P = .017$); this did not vary by study.

#### Vaccine Efficacy Against COVID-19: PWH

Applying the same modeling strategy to examine the effect of HIV on hazard of COVID-19 yielded similar results (Table 5). There was no significant interaction between HIV and vaccination ($P = .403$) on symptomatic COVID-19, indicating a lack of evidence that the VE was different between participants with HIV compared with participants without HIV for any of the studies. Unlike the primary results, there was also not a significant main effect of HIV among the placebo recipients ($P = .608$). Because of sample size limitations of PWH, the effect of HIV on vaccine efficacy for the severe COVID-19 clinical endpoint could not be assessed.

Because a large proportion of the TIS analysis set comprised individuals with diabetes, we fit the same type of models using an indicator of diabetes as the key predictor. The results were very similar to those derived from models using the TIS indicator. Finally, we refit the model to evaluate the association of TIS with symptomatic COVID-19, but only among the participants that did not have diabetes. These results were generally consistent, though with the smaller numbers of TIS participants the confidence intervals are substantially wider. The results of both investigations are presented in Supplementary Table 7.

## DISCUSSION

Our study is unique in that we defined a category of individuals with mild immunosuppression and subsequently used that variable in a cross-protocol analysis of 4 harmonized, placebo-controlled, randomized efficacy trials of distinct COVID-19 vaccine platforms and across different sponsors. Our analysis fills an important knowledge gap of COVID-19 VE in individuals living with mild immunocompromising conditions. We demonstrated that there was no evidence of statistical difference in VE against COVID-19 or severe COVID-19 in participants with TIS compared with those with NTIS. Receiving the study vaccine (across all 4 studies) compared with placebo resulted in significantly decreased likelihoods of developing symptomatic or severe COVID-19. In addition, individuals living with well-controlled HIV on antiretroviral therapy had similar COVID-19 VE compared with those without HIV. Thus, despite immune modulation and relative immunodeficiencies, all 4 COVID-19 vaccines had robust protection against symptomatic or severe COVID-19. Furthermore, the consistent findings across all 4 sponsors speak to the robustness of our conclusions.

Immunocompromising conditions exist on a spectrum, with varying degrees of immunosuppression based on the underlying disease and/or immunomodulatory therapy. For example, the receipt of B-cell–depleting therapies or mycophenolate mofetil severely limits vaccine-induced immunogenicity [5, 26, 27]. However, individuals receiving these therapies are on the extreme

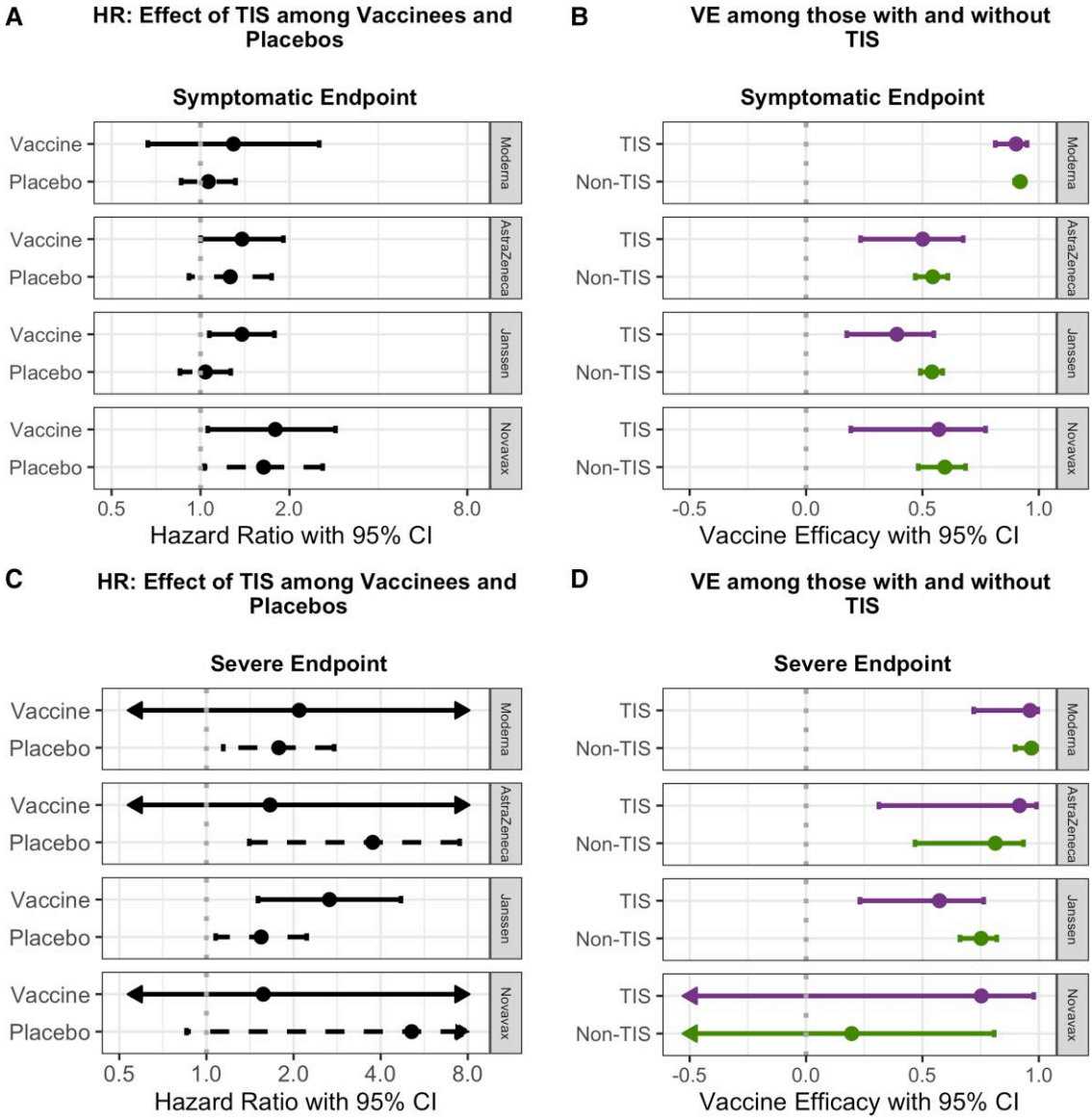


**Figure 2.** Hazard ratios (HR) and vaccine efficacy (VE) for the full analysis set. *A*, HR and (*B*) VE for each trial for the symptomatic coronavirus disease 2019 (COVID-19) endpoint. *C*, HR and (*D*) VE for each trial for the severe COVID-19 endpoint. For HR (*A* and *C*), the participants receiving vaccine (solid black line) versus placebo (dashed black line) are described for each trial. For VE (*B* and *D*), participants with TIS (tempered immune system, purple) and non-TIS (green) are described for each trial. Please refer to Supplementary Table 5 for further details.

end of this immunocompromised spectrum. Less is understood about VE in individuals with more subtle immune defects or intermittent use of immunomodulatory therapies. Our study demonstrates that individuals having diabetes, having a history of solid neoplasms and/or chemotherapy within 2 years of the vaccination, receiving low doses of prednisone, receiving biologics, and/or fitting any of the other terms described in our TIS definition are still able to mount protective responses against symptomatic and severe COVID-19. We also found no difference in the VE against symptomatic SARS-CoV-2 infection in PWH compared with those without HIV, which supports existing literature on immunogenicity and VE in PWH on antiretroviral therapy with virologic control. Other cohort studies have reported immunogenicity as stratified by CD4 count and demonstrated that PWH with CD4 count <200 cells/μL had lower detectable SARS-CoV-2 receptor-binding domain–binding immunoglobulin G at 86.7% (26/30), compared with 100% detectable receptor-binding domain–binding immunoglobulin G for those with a CD4 count of 200 to 500 cells/μL (53/53) or >500 cells/μL (168/168) [28]. Although we did not report immunogenicity in our study, the strong VE observed in our cohort of PWH supports the finding that robust and functional SARS-CoV-2 antibodies can be induced in individuals with

**Table 5. Symptomatic COVID-19 Endpoint in PWH, Full Analysis Population**

| Vaccine Efficacy (95% CI) | Non-PWH | PWH |
|---|---|---|
| Moderna | 0.918 (0.896–0.936) | 0.754 (−1.200 to 0.973) |
| Novavax | 0.588 (0.480–0.674) | 0.866 (−0.285 to 0.986) |
| AstraZeneca | 0.535 (0.463–0.598) | 0.753 (0.264–0.917) |
| Janssen | 0.535 (0.485–0.579) | 0.135 (−0.623 to 0.539) |
| HR: PWH versus non-PWH | Placebo | Vaccinated |
| Moderna | 1.019 (0.381–2.730) | 3.072 (0.427–22.116) |
| Novavax | 3.338 (1.064–10.466) | 1.083 (0.151–7.749) |
| AstraZeneca | 1.855 (0.956–3.597) | 0.984 (0.407–2.381) |
| Janssen | 0.729 (0.472–1.125) | 1.354 (0.845–2.170) |
| *P* values from analysis of deviance in Cox model | | |
| PWH versus non-PWH | 0.608 | |
| Interaction between PWH and study | 0.326 | |
| Interaction between PWH and vaccine | 0.403 | |
| Interaction between PWH, vaccine, and Study | 0.112 | |

The Cox proportional hazards model was adjusted for age, sex, race, study, baseline SARS-CoV-2 status, and allowed for a different vaccine efficacy for each study. The severe COVID-19 endpoint was not evaluated in the HIV population because of limited sample size. *P* value from F test.

Abbreviations: CI, 95% confidence interval; COVID-19, coronavirus disease 2019 HR, hazard ratio; PWH, people with HIV; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

well-controlled HIV. Of note, baseline CD4 count data were not collected across the 4 vaccine clinical trials; however, CD4 levels had to be at least ≥200 cells/μL to meet eligibility criteria for 3 of the 4 trials (CD4 eligibility described in the Supplementary Table 1).

Clinical correlates of protection for COVID-19 have been described [29] but need to be further defined. These measures in immunocompromised individuals have important consequences in establishing recommendations for dosing, timing, and interval of COVID-19 vaccination to prevent severe COVID-19 and related complications. The spectrum of immune-compromising conditions must be addressed in vaccine guidelines and recommendations. As new immunomodulatory drugs become available, it will be important to continuously redefine the impact of these treatments on vaccine-induced responses.

Our study has several limitations. The TIS group was defined post hoc, and thus is subject to postrandomization bias; however, it was defined blinded to treatment and outcomes. There is also variability in the degree of immunosuppression within the TIS group, given that some conditions or medications likely impact the immune system more than others. Since metabolic and nutritional disorders represented the large majority of TIS conditions, our results cannot be generalized to all other potentially immunocompromising conditions. Furthermore, clinical trial participants are generally healthy, with fewer comorbidities, and may be more adherent to appointments or medications, and thus may have relatively mild features of immune dysregulation (eg, well-controlled HIV with virologic suppression, adequate CD4 counts), which can lead to limited generalizability and bias. We did not analyze the cohorts by other comorbidities (eg, cardiac disease, liver disease); however, no differences in COVID-19 VE by comorbidities were described across the phase 3 COVID-19 vaccine trials in a dedicated analysis [30]. Duration of immunocompromising medical conditions or medication beyond the time of enrollment was not analyzed, which could have led to misclassification as NTIS from an undiagnosed condition present at enrollment.

Furthermore, the analysis presented here used data only from the primary vaccine series of these initial trials, which occurred early in the COVID-19 pandemic. Few participants would have had prior SARS-CoV-2 infection, and our analysis also does not include booster doses or updated variant vaccines. Our results are applicable only to the circulating variants present during the blinded phase of each trial (eg, do not include the Delta or Omicron waves) and there are also limitations with regard to timepoint of analysis influencing our interpretation of durability of protection. We did not directly compare VE for TIS by vaccine platform because of differences in timing of the trials (with different variants circulating) as well as variations in baseline characteristics and eligibility criteria that could bias results. Most importantly, we were not able to control for SARS-CoV-2 exposure risk heterogeneity considering that the TIS group may have practiced increased protective behavior such as masking and avoidance of indoor spaces. Anxieties were evident among certain populations of immunocompromised individuals early in the pandemic [31], which may have caused these individuals to increase precautions and motivated them to participate in clinical trials. Regardless, our study is the largest compilation of individuals with defined immune suppressive conditions in whom VE was carefully defined prospectively.

## CONCLUSIONS

As expected, those with TIS had greater risk for severe COVID-19 compared with those with NTIS, underscoring the importance of vaccination to reduce the risk of severe disease in this population. The finding of an overall increased hazard of severe COVID-19 among those with TIS compared with those without suggests our definition appropriately identified participants enrolled in the phase 3 studies with mild immunosuppression. Notably, our findings demonstrate that there is no statistical evidence of any difference in primary COVID-19 vaccine efficacy in those with TIS compared with those with NTIS across the 4 COVID-19 vaccine platforms analyzed (Moderna, AstraZeneca, Janssen, and Novavax) in efficacy

trials. Additionally, there was no significant difference in symptomatic SARS-CoV-2 infection in PWH who received primary COVID-19 vaccination, relative to those without HIV, suggesting that individuals with well-controlled HIV can mount protective responses to SARS-CoV-2 after vaccination. Our analyses highlight the nuanced subtleties of those with relatively mild immunocompromised status compared with those with intact immune systems and support the use of COVID-19 vaccines for this population.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Acknowledgments.*** We thank Samuel Robinson for helpful discussion and Nicole Na for administrative support. We also acknowledge and thank the trial participants, caregivers, investigators, healthcare providers, and research staff who contributed to the 4 trials.

***Financial support.*** The COVID-19 Phase 3 trials were supported by US government funding through the Biomedical Advanced Research and Development Authority (BARDA) and National Institute of Allergy and Infectious Diseases (NIAID). The CoVPN network was formed through a partnership of multiple existing NIAID-funded clinical trial networks, including the HIV Vaccine Trials Network (HVTN), Vaccine Treatment and Evaluation Units (VTEUs), the HIV Prevention Trials Network (HPTN), the AIDS Clinical Trials Group (ACTG), and the Infectious Diseases Clinical Research Consortium (IDCRC). In particular, this work was supported by National Institutes of Health UM1 AI068614 to L. C. for CoVPN Operational Infrastructure; UM1 AI068635 to P. B. G., Y. H., and H. E. J. for CoVPN cross-protocol statistical analyses; UM1 AI069412 to L. R. B.

***Potential conflicts of interest.*** O. A. received salary support from research funding paid to UCLA by Moderna, Inc. A. T. reports that this project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. 75N91019D00024. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. C. L. G.'s institution received funding from the NIH for salary support for her role as site Principal Investigator for the Moderna Phase 3 trial and site Principle and Co-Chair for the Novavax Phase 3 trial. N. R. received research grants from Pfizer, Merck, Sanofi, Quidel, Immorna, Vaccine Company, and Lilly through her institution, consulting fees from Krog, honoraria as speaker for Virology education, and travel support from Sanofi and Moderna. N. R. serves on safety committees for ICON and EMMES and is a member of the Moderna, Sanofi, Seqirus, and Pfizer selected Advisory boards. I. H. is an employee of AstraZeneca and holds/may hold stock in AstraZeneca. A. R. F. reports grant support from Janssen, Pfizer, Moderna, CyanVac, VaxCo, and BioFire Diagnostics; advisory board fees from Arrowhead and GSK; travel reimbursement from GSK and Sanofi and fees for DSMB from Novavax. B. L. is an employee of Moderna, Inc. and may own stock/stock options in the company. J. S. declares support for the submitted work from the Janssen Pharmaceutical Companies of Johnson & Johnson and partial support (in the form of funding to his institution) from BARDA for the submitted work, declares support from the Janssen Pharmaceutical Companies of Johnson & Johnson and BARDA funding for part of this work, has patents on invention of the Janssen COVID-19 vaccine, and has Johnson & Johnson stock and stock options. P. A. G. reports a patent for a COVID-19 monoclonal antibody from Aridis Pharmaceuticals. V. C. reports payments made to Emory University from Gilead Sciences. K. N. receives grants from NIH to participate in overall organization of COVID vaccine trials and for participation in vaccine trials and has a grant for Vaxco for a phase 1 testing of a broadly reactive COVID-19 vaccine. L. D. is an employee of Novavax, Inc. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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