Biomedicine & Pharmacotherapy 192 (2025) 118663

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Sex and age-related differences in humoral and cellular responses to the recombinant zoster vaccine in people living with HIV

Cristina Díez [a,b,c,1], Carlos Pita-Martínez [d,1], Marta Quero-Delgado [b,d,1], Aurora Gómez-Tórtola [a], Chiara Fanciulli [a,b,c], Ana Marchan [d], Teresa Aldámiz-Echevarría [a,b,c], Daniel Sepúlveda-Crespo [b,d], Francisco Tejerina [a,b,c], Leire Pérez-Latorre [a,b,c], Isabel Gutiérrez [c], Juan Carlos López [a,b,c], Isidoro Martínez [b,d,*,1], Salvador Resino [b,d,*,2]

[a] Unidad de Enfermedades Infecciosas/VIH, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[b] Centro de Investigación Biomédica en Red en Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain
[c] Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[d] Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain

ARTICLE INFO

Keywords:
HIV
Recombinant Zoster Vaccine
Immunogenicity
Aging
Sex

ABSTRACT

Background: Data on the immunogenicity of the recombinant zoster vaccine (RZV) in people living with HIV (PLWH) are limited, despite their high risk for herpes zoster. This study aimed to characterize the humoral (Varicella-zoster virus (VZV)-specific IgG) and cellular (VZV-specific IFN-γ/IL-2 T-cell) immune responses to RZV in PLWH on suppressive antiretroviral therapy (ART), stratified by sex and age.

Methods: This prospective study enrolled 207 PLWH on suppressive ART who received two doses of RZV. VZV-specific IgG antibody titers were quantified by in-house ELISA at baseline and post-vaccination and T-cell responses using FluoroSpot assays post-vaccination. We estimated geometric mean titers (GMTs), geometric mean fold rises (GMFRs), and adjusted arithmetic mean ratios (aAMRs) using generalized linear models.

Results: RZV vaccination induced a significant humoral response, with an overall GMFR of 16.7 and a 71 % positive response rate (≥4-fold rise in IgG titers). Females < 60 years old exhibited a markedly higher GMFR (43.8) than all other subgroups ($p < 0.05$). The vaccine also induced robust VZV-specific T-cell responses, with GMTs being comparable across all groups. Notably, a strong positive association was found between humoral and T-cell responses, particularly with IL-2-secreting cells (aAMR=1.6, $p < 0.001$). This association was most pronounced in participants < 60 years, especially females, and was attenuated in older individuals.

Conclusions: RZV vaccination effectively induces both humoral and T-cell immunity in PLWH. However, host factors, such as sex and age, critically modulate immunogenicity. Females < 60 years showed a superior humoral response and the strongest association between immune compartments, highlighting important variability in vaccine responsiveness.

1. Introduction

Varicella-zoster virus (VZV) is the etiological agent of both varicella (chickenpox) and herpes zoster (HZ) [1]. Following primary infection, VZV establishes latency in the sensory ganglia. HZ results from the reactivation of latent VZV, which normally occurs when cell-mediated immunity wanes due to aging or immunosuppression. HZ is often accompanied by severe neuropathic pain and complications such as

* Correspondence to: Centro Nacional de Microbiología, Instituto de Salud Carlos III, Carretera Majadahonda, Pozuelo, Km 2.2, Madrid, Majadahonda ES-28220, Spain.

E-mail addresses: crispu82@gmail.com (C. Díez), carlos.pita@isciii.es (C. Pita-Martínez), marta.quero@isciii.es (M. Quero-Delgado), aurora.gomez@salud.madrid.org (A. Gómez-Tórtola), Fanciulli.chiara@gmail.com, marchancarrascoana@gmail.com (C. Fanciulli), teresaldamiz@yahoo.es (T. Aldámiz-Echevarría), daniel.sepulveda@isciii.es (D. Sepúlveda-Crespo), franciscotejerina@gmail.com (F. Tejerina), legor78@hotmail.com (L. Pérez-Latorre), isabelgutierrezcuellar@hotmail.com (I. Gutiérrez), juanclopezbq@gmail.com (J.C. López), imago@isciii.es (I. Martínez), sresino@isciii.es (S. Resino).

[1] These first authors contributed equally to this article
[2] These senior authors contributed equally to this article

https://doi.org/10.1016/j.biopha.2025.118663
Received 4 August 2025; Received in revised form 14 October 2025; Accepted 17 October 2025
Available online 21 October 2025

postherpetic neuralgia [1]. The lifetime risk of developing HZ is approximately 30 %, and its incidence increases markedly after the age of 50 years [2].

The immune response to VZV involves both innate and adaptive mechanisms [3]. Innate immunity is triggered by toll-like receptor recognition of viral components, leading to the production of interferon (IFN) and pro-inflammatory cytokines. Natural killer cells, dendritic cells, and monocytes play key roles in viral control. Adaptive immunity is characterized by CD4 + and CD8 + T cell responses to viral antigens, such as glycoprotein E (gE), alongside B cell production of VZV-specific antibodies [3].

Vaccination against VZV has proven effective in reducing the disease burden and preventing HZ. Both live attenuated vaccines (e.g., Variax®) and the adjuvanted recombinant zoster vaccine (RZV; e.g., Shingrix®) provide protective immunity [3,4]. While live attenuated zoster vaccines are contraindicated in immunocompromised populations [5], the adjuvanted RZV (Shingrix®), containing a VZV glycoprotein E antigen and the AS01B adjuvant system, has been shown to elicit strong and durable immune responses [6,7], and has proven to be safe and effective in reducing the risk of herpes zoster in these immunocompromised individuals [8].

Despite the success of combination antiretroviral therapy (ART) in suppressing viral replication and facilitating immune reconstitution [9], people living with HIV (PLWH) often exhibit incomplete immune recovery. This leaves them with persistent deficits in cellular immunity, chronic inflammation, and a higher risk of non-AIDS comorbidities [9,10]. This enduring vulnerability is clinically exemplified by the notably higher incidence of herpes zoster and postherpetic neuralgia in PLWH compared to the age-matched general population [11,12]. This elevated risk is attributed to the same underlying immune dysfunction that persists despite effective ART, which is characterized by chronic immune activation and suboptimal vaccine responsiveness. [13].

RZV is approved in Europe for adults aged $\geq$ 50 years and for immunocompromised individuals aged $\geq$ 18 years [10,14]. Although recent studies have shown that RZV induces strong and durable humoral and cellular immune responses in PLWH [7,13,14], several knowledge gaps remain. To our knowledge, no studies have yet investigated the influence of key host factors, such as sex and age, on RZV immunogenicity in PLWH. Therefore, a deeper understanding of how these factors modulate vaccine responses is crucial for optimizing vaccination strategies in this vulnerable group.

1.1. Objective

We aimed to characterize both humoral (VZV-specific IgG) and cellular (VZV-specific IFN-γ/IL-2 secreting T-cells) immune responses to RZV in PLWH on ART, stratified by sex and age groups.

2. Materials and methods

2.1. Design and study population

We conducted a prospective, single-center study at the Hospital General Universitario Gregorio Marañón (HGUGM) in Madrid, Spain, between August 2023 and October 2024. The inclusion criteria for participants were: PLWH on ART, aged > 18 years; an undetectable HIV viral load (<30 copies/mL); no prior vaccination with RZV; and provision of written informed consent. Key exclusion criteria included a history of severe allergic reaction to any component of the vaccine, pregnancy or breastfeeding, and the presence of an acute, moderate-to-severe illness at the time of enrollment.

The vaccination regimen consisted of two 0.5-mL intramuscular (IM) injections of the RZV (Shingrix®). Participants received two doses of RZV administered two months apart (baseline on day 0 and the second dose on approximately day 60), following the manufacturer's recommended schedule, which is consistent with national clinical guidelines for this vaccine. The final follow-up visit was scheduled for day 120 (four months after the first dose and two months after the second). All injections were administered into the deltoid muscle.

The study protocol and informed consent form were approved by the HGUGM Ethics Committee (Ref: MICRO.HGUGM.2023–08), and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Clinical data and samples

Clinical data were retrieved from the hospital's electronic medical records and managed using REDCap (Research Electronic Data Capture), a secure web-based platform developed by Vanderbilt University (Nashville, TN, USA) [15].

Peripheral blood samples were collected by venipuncture into EDTA-containing tubes at baseline (day 0) and at the final follow-up visit on day 120 (two months after the second vaccine dose). Plasma and peripheral blood mononuclear cells (PBMCs) were then separated from whole blood using Ficoll gradient centrifugation. Plasma aliquots were stored at −80°C, while PBMCs were cryopreserved in liquid nitrogen until further analysis.

2.3. Quantification of humoral immune response to RZV

IgG antibody titers to VZV glycoprotein E (anti-gE IgG) were measured using an in-house indirect ELISA at both baseline and post-vaccination. Briefly, 96-well microplates were coated with 0.2 μg per well of recombinant gE from VZV Oka strain (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. 15915219) and incubated overnight at 4ºC. The following day, plates were blocked for 1 h at room temperature with PBS containing 0.05 % Tween-20 supplemented with 5 % pig serum (SC; Gibco™, Penrose, Auckland, New Zealand). Plasma samples, serially diluted 1:3, starting from a 1:20 dilution down to a final dilution of 1:14580 in the same blocking buffer, were added and incubated for 1 h at room temperature. After the plate was washed with PBS, a peroxidase-conjugated secondary antibody specific for human IgG (Jackson ImmunoResearch, West Grove, PA, USA) was added and incubated for 30 min in the dark at room temperature. Following a final washing step, the OPD substrate (Sigma Aldrich, San Luis, MO, USA) was added. The reaction was allowed to develop for approximately 3 min before being stopped with 3 N sulfuric acid. A VZV-positive serum sample from a donor with a high IgG titer, initially validated with a commercial immunoassay (Human VZV IgG ELISA Kit, MyBiosource, San Diego, CA, USA) and also quantified with our in-house ELISA, was used as a positive control for inter-plate normalization.

The AUC, representing the magnitude of the IgG response. Seropositivity was defined by a cut-off value calculated from the mean optical density of blank wells (the first sample dilution without antigen) plus three standard deviations. A sample was classified as seropositive if the signal from its first dilution (1:20) exceeded this threshold, and its AUC was subsequently calculated. Samples with a signal below this cut-off were considered seronegative. To ensure consistency and enable natural log (ln) transformations and ratio calculations, a constant of 0.1 units was added to all AUC measurements.

2.4. Quantification of cellular immune response to RZV

Cellular immune responses were evaluated using a FluoroSpot Plus Human IFN-γ/IL-2 kit (Mabtech Inc., Cincinnati, OH, USA). In pre-coated 96-well plates, 300,000 PBMCs were seeded per well in a base medium of RPMI (supplemented with P/S, L-Gln, and FBS) containing 1 μg/mL of anti-CD28 mAb as a co-stimulus. For specific stimulation, VZV glycoprotein E (gE) peptide pools [gE Oka pool SB285–15NM (sb-peptide, Saint Egrève, France)] were added at a final concentration of 0.2 μg/mL per peptide. The peptide pool consisted of 123 synthetic peptides, each 15 amino acids in length and overlapping by 11 amino

acids. Positive control wells received anti-CD3 mAb (0.2 μg/mL), and negative control wells received medium alone, both with the anti-CD28 co-stimulus. Following an 18-hour incubation at 37°C and 5 % CO2, plates were washed, and a combination of biotin-conjugated anti-IL-2 and BAM-labeled anti-IFN-γ detection antibodies was added. After a subsequent wash, spots were visualized with Cy3-conjugated streptavidin and FITC-conjugated anti-BAM. Plates were read using an AID iSpot ELISpot FluoroSpot Reader (AID GmbH). Final counts were expressed as spot-forming cells (SFCs) per million PBMCs after subtracting the background from negative control wells. The general FluoroSpot procedure was adapted from the methodology described in Muñoz-Gómez et al. [16].

2.5. Outcome variables

The primary outcome for the humoral response was the area under the curve (AUC), which represents the magnitude of the anti-gE IgG response. Based on this outcome, several endpoints were defined: i) Seropositivity: A participant was considered seropositive at baseline if their AUC was above a pre-defined cut-off (0.1). ii) Positive Humoral Response: Defined as a ≥ 4-fold increase in AUC from baseline. This is a conventional threshold in vaccinology, widely used to define a significant serological response that accounts for assay variability and is consistent with the endpoints used in pivotal vaccine licensure trials [17, 18]. iii) Seroconversion: For participants who were seronegative at baseline, this was defined as achieving a post-vaccination AUC above the 0.1 cut-off.

The primary outcome for the cellular immune response was the number of VZV gE-specific spot-forming cells (SFCs) per million peripheral blood mononuclear cells (PBMCs), quantified post-vaccination. This was assessed for three distinct T-cell functions: i) IFN-γ-secreting cells. ii) IL-2-secreting cells. iii) Polyfunctional cells co-secreting both IFN-γ and IL-2.

2.6. Statistical analysis

Statistical analyses were performed using Stata version 18.0 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Figures were generated with GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). A two-tailed p-value < 0.05 was considered statistically significant. For all generalized linear models (GLMs), parameter estimates, standard errors of the mean (s.e.m.), and 95 % confidence intervals (CIs) were derived using a non-parametric bootstrap method with 1000 replicates and bias-corrected and accelerated (BCa) intervals.

To evaluate the magnitude of the humoral response, geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) were estimated using GLMs with a Gaussian family and identity link, fitted to ln-transformed data. Study groups defined by sex and age (<60 vs. ≥60 years) were included as predictors in the models. GMTs and GMFRs for each sex/age group and the overall cohort were obtained by exponentiating the predictive margins (*margins* command), and differences between groups were calculated using the *lincom* command with the *eform* option. To identify baseline factors associated with achieving a positive humoral response (defined as a ≥4-fold increase in anti-gE IgG titers), we fitted a GLM with a binomial distribution and a log link function, using robust standard error estimates. The resulting exponentiated coefficients provided the risk ratios (RRs) for each baseline characteristic.

The association between VZV-specific T-cell responses and the post-vaccination humoral response was assessed using a GLM with a gamma family and a log link. In these models, ln-transformed spot-forming cells (SFCs) for IFNγ, IL-2, and IFNγ/IL-2 served as the independent variables, while post-vaccination VZV IgG levels were the dependent variable. These models yielded an arithmetic mean ratio (AMR), representing the multiplicative change in the humoral response per unit increase in the T-cell response.

For all GLM analyses, models were run in two forms: unadjusted (bivariate models with only the primary predictor, sex/age group) and adjusted by a pre-defined set of covariates selected *a priori* based on their established clinical significance as potential confounders in PLWH. Specifically, the models included: (1) baseline CD4 + T-cell count, to reflect current immune status; (2) prior AIDS diagnosis, to account for the impact of historical immunosuppression; (3) time on ART, to reflect the duration of viral suppression and immune reconstitution; and (4) sexual transmission of HIV, as a primary epidemiological characteristic that can be associated with other host factors.

3. Results

3.1. Patient characteristics

A total of 207 participants were included in the study. The baseline characteristics of the cohort are presented in Table 1. In brief, most participants were male (164/207; 79.2 %), and the median age was 56.4 years. Regarding geographic origin, 160 (77.3 %) were European, and 43 (20.8 %) were Latin American. The primary route of HIV acquisition was sexual transmission (109/207; 52.7 %). The median nadir CD4 + count was 227.5 cells/mm^3 , 43 participants (20.8 %) had prior AIDS-defining conditions, and 22 (10.6 %) reported a previous history of herpes zoster. At baseline, all participants were on ART with an undetectable HIV viral load and a median CD4 + cell count of 815 cells/mm^3 .

Table 1 also details the characteristics of the study population stratified by sex and age. The groups comprised males under 60 years (n = 115, 55.6 %; median age 49.8 years), males 60 years or older (n = 49, 23.7 %; median age 62.4 years), females under 60 years (n = 29, 14.0 %; median age 56.4 years), and females ≥ 60 years (n = 14, 6.8 %; median age 63.8 years).

3.2. Humoral immune response to the RZV

At baseline, 37.7 % (78/207) of participants were seropositive for anti-gE IgG. RZV vaccination induced a significant increase in humoral immunity, with the overall GMT rising from 0.7 ± 0.1 at baseline to 10.5 ± 1.7 post-vaccination, resulting in a GMFR of 16.7 ± 3.8. Based on the fold-rise from baseline, 71 % (147/207) of participants mounted a positive humoral response (defined as a ≥4-fold rise in IgG titers). The remaining participants showed either a < 4-fold rise (11.6 %; 24/207) or no increase in antibody titers (17.4 %; 36/207). Importantly, none of the baseline clinical or epidemiological characteristics analyzed were significantly associated with failing to mount a positive response (*data not shown*).

Stratifying the analysis by sex and age, we found that baseline GMT values were similar across sex and age groups (Fig. 1A). However, post-vaccination, females < 60 years (22.9 ± 8.7) exhibited higher GMTs compared to females ≥ 60 years (5.1 ± 3.3; p = 0.043), males ≥ 60 years (9.1 ± 2.8; p = 0.063), and males < 60 years (8.6 ± 1.7; p = 0.026) (Fig. 1B). Similarly, the GMFR was also significantly higher in females < 60 years (43.8 ± 21.6) compared to females ≥ 60 years (7.8 ± 3.8; p = 0.008), males ≥ 60 years (10.9 ± 4.4; p = 0.028), and males < 60 years (13.4 ± 3.8; p = 0.038) (Fig. 1**C**). Thus, while vaccination enhanced humoral responses in all groups, females under 60 years showed a particularly robust response.

In a multivariable analysis adjusted for potential confounders, the significant differences in GMFR between groups were maintained. In contrast, the observed differences in post-vaccination GMTs lost statistical significance (Supplementary Table 1).

3.3. T-cell immune response to the RZV

Approximately two months following the second vaccine dose, the GMT values for VZV-specific T-cell responses were 115.6 ± 10.7 for IFN-γ secretion, 205.9 ± 14.2 for IL-2 secretion, and 57.5 ± 5.0 for dual IFN-

Table 1
Epidemiological and clinical characteristics of the study population, people with HIV vaccinated against VZV.

		Male		Female	
	All	**< 60 years**	**≥ 60 years**	**< 60 years**	**≥ 60 years**
No.	207	115	49	29	14
Age (years)	56.4 (45.7–60.7)	49.8 (39.7–56.2)	62.4 (61.1–65.3)	56.4 (52.8–57.9)	63.8 (60.9–67.9)
Males	164 (79.2)	-	-	-	-
Origin					
Europe	160 (77.3)	77 (67)	46 (93.9)	25 (86.2)	12 (85.7)
Latin America	43 (20.8)	35 (30.4)	3 (6.1)	4 (13.8)	1 (7.1)
Others	4 (1.9)	3 (2.6)	-	-	1 (7.1)
HIV Acquisition					
Sexual	109 (52.7)	74 (64.3)	17 (34.7)	12 (41.4)	6 (42.9)
IDU	34 (16.4)	17 (14.8)	11 (22.4)	5 (17.2)	1 (7.1)
Others	3 (1.4)	1 (0.9)	-	2 (6.9)	-
Unknown	61 (29.5)	23 (20)	21 (42.9)	10 (34.5)	7 (50)
Nadir CD4$^+$ (cells/mm^3)	227.5 (149–400)	300 (180–491)	199 (90–307)	215 (118–336)	188 (122.5–262)
Baseline CD4$^+$ (cells/mm^3)	815 (610–1055)	826 (703–1100)	715 (482–933)	930 (591–1172)	907 (500–1015)
Prior AIDS diagnosis	43 (20.8)	18 (15.7)	14 (28.6)	7 (24.1)	4 (28.6)
Immunosuppression therapy	12 (5.8)	8 (7)	4 (8.2)	-	-
Previous HZ episode	22 (10.6)	7 (6.1)	10 (20.4)	3 (10.3)	2 (14.3)

Statistics: Values are expressed as absolute counts (percentages) for categorical variables and as medians (P25th – P75th) for continuous variables. **Abbreviations:** HIV, human immunodeficiency virus; IDU, intravenous drug use; AIDS, acquired immunodeficiency syndrome; HZ, herpes zoster; VZV, varicella-zoster virus.

γ/IL-2 secretion. Statistical analysis revealed no significant differences in these post-vaccination GMT values related to sex or age across all three cytokine secretion assays (Supplementary Table 2). Consequently, post-vaccination T-cell responses were comparable across sex and age groups. The lack of a statistically significant association persisted after adjustment for potential confounders (Supplementary Table 2).

3.4. Association between humoral and T-cell responses to the RZV

A significant positive association was identified between the magnitude of the post-vaccination humoral response and VZV-specific T-cell responses across all functional subsets (Fig. 2; see Supplementary Table 3 for a full description). In the overall cohort (Fig. 2A), higher IgG levels were strongly associated with higher frequencies of IFN-γ-secreting cells (aAMR=1.3; $p = 0.018$), IL-2-secreting cells (aAMR=1.6; $p < 0.001$), and polyfunctional IFN-γ/IL-2-secreting T-cells (aAMR=1.3; $p = 0.009$).

This association, however, was critically modulated by sex and age. The association was most pronounced and consistent in females < 60 years, who demonstrated robust associations across all three T-cell profiles (Fig. 2D; all $p < 0.005$), peaking with IL-2-secreting cells (aAMR=1.7; $p < 0.001$). Males < 60 years also exhibited a solid, coordinated response, with all T-cell subsets showing a significant association with humoral immunity (Fig. 2B; all $p < 0.04$). In contrast, this interplay was markedly attenuated in the older strata. Both males and females aged ≥ 60 years (Fig. 2C and E, respectively) only retained a statistically significant association for the IL-2-secreting T-cell subset.

4. Discussion

In this real-world cohort study, we evaluated humoral and VZV-specific T-cell immune responses following RZV vaccination in PLWH on ART with undetectable viral loads. Vaccination significantly enhanced humoral immunity, as demonstrated by increased GMTs and GMFRs. Notably, post-vaccination GMTs and GMFRs were substantially higher in females < 60 years of age despite comparable baseline titers across all subgroups. The vaccine also induced robust VZV-specific T-cell responses (IFN-γ, IL-2, and dual IFN-γ/IL-2 secretion), though these T-cell GMTs did not differ significantly by sex or age. Importantly, we observed a positive association between the magnitude of T-cell responses (particularly those involving IL-2 and IFN-γ/IL-2) and the humoral response in the overall cohort, with this association being most pronounced and consistent in females < 60 years.

The RZV, based on glycoprotein E, is known for its high immunogenicity in adults, inducing both robust VZV-specific antibody production and CD4 + T-cell responses that are associated with stable, long-term protection [7,19–21]. However, as RZV was only recently licensed for use in immunocompromised patients, there is a paucity of data in the literature regarding its efficacy, immunogenicity, and safety in PLWH [14]. Despite effective ART leading to viral suppression and CD4 + T-cell recovery, PLWH remain at a significantly increased risk of developing herpes zoster and postherpetic neuralgia compared to the general population [11,12,22]. Both cellular and humoral immune responses are pivotal in controlling VZV infection and preventing its reactivation [7,23]. Specifically, robust VZV-specific T-cell responses are associated with limiting viral replication and reducing the incidence and severity of herpes zoster [23], while VZV-specific antibodies contribute to protection by neutralizing the virus and facilitating the clearance of infected cells, partly through mechanisms like antibody-dependent cellular cytotoxicity [24].

In our cohort of PLWH, the humoral response rate following vaccination was 71 % (defined as a ≥4-fold rise in anti-gE antibody levels). While this represents a substantial immunogenic effect, this rate is lower than the > 95 % response typically observed in the general population [18–20]. Although the quantitative response in our cohort was lower than that reported in healthy populations, the vaccine still elicited a robust immunogenic effect in the majority of participants. This aligns with the broader understanding that even when RZV produces attenuated humoral and T-cell responses in immunocompromised individuals, it still provides clinically meaningful increases in both arms of the immune system, conferring significant protection [25,26].

This attenuated effect of the vaccine likely reflects the impact of persistent immune dysfunction inherent to the PLWH population, a finding consistent with reports of attenuated responses in other immunocompromised groups (e.g., 77.6 % in cancer patients) compared to healthy controls [7]. However, this result cannot be attributed solely to HIV-related immunodeficiency. Notably, pivotal Phase I/IIa clinical trials of RZV in PLWH reported humoral response rates exceeding 90 % [27], suggesting that other factors may be at play. One key methodological difference is the timing of the assessment. Peak immunogenicity is typically observed one month post-vaccination, whereas our responses were measured at two months, potentially capturing the initial decline of antibody levels [28]. Furthermore, host-specific factors such as sex and age also influence immunogenicity. For instance, vaccine responses in older adults, while still high, are known to be lower than in younger populations [29]. Moreover, vaccine-induced antibody responses are

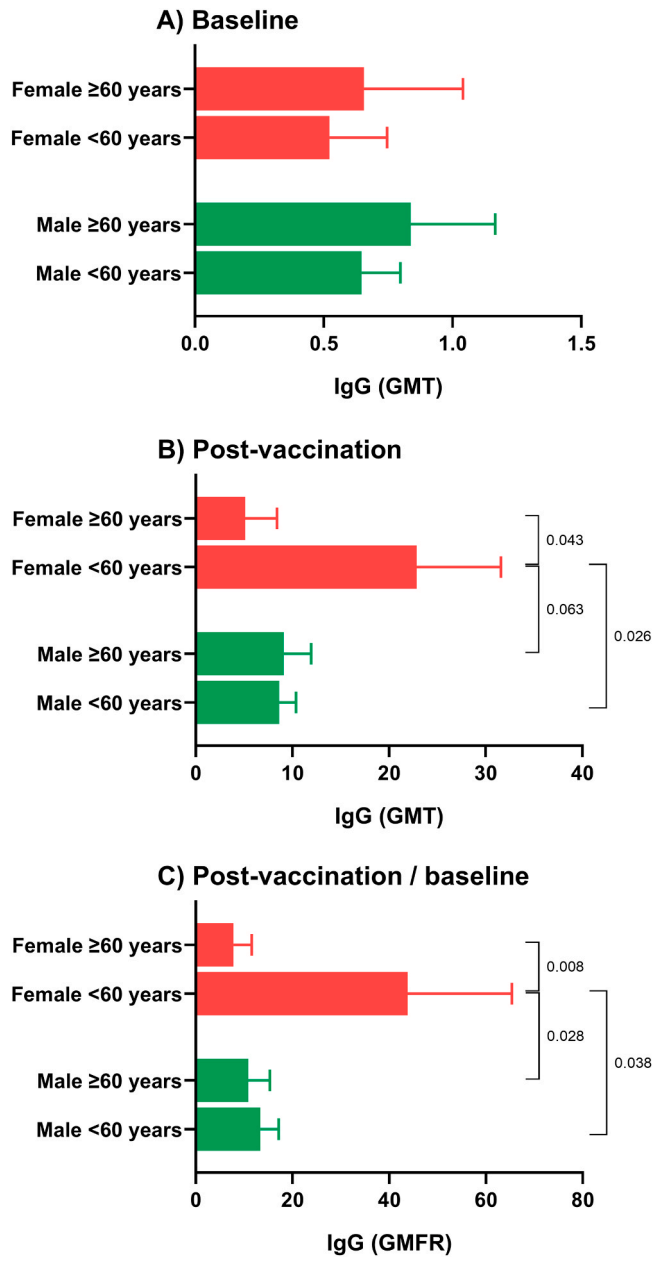


Fig. 1. VZV-specific IgG response to vaccination in people with HIV, stratified by sex and age. The figure displays key metrics of the VZV-specific IgG response: (A) baseline geometric mean titers (GMTs), (B) post-vaccination GMTs, and (C) geometric mean fold rises (GMFRs) from baseline. Data are presented as GMT or GMFR ± s.e.m. for each subgroup. P-values represent the statistical comparison between the indicated groups from unadjusted models. In panels B and C, p-values denote the comparison of each group against the 'Female < 60 years' group. **Statistics**: GMTs and GMFRs were estimated from generalized linear models fitted to the ln-transformed area under the curve (AUC) data and represent exponentiated predictive margins. P-values were derived from the same models using post-estimation commands. The standard error of the mean (s.e.m.) was derived via a non-parametric bootstrap (1000 replicates, BCa method). **Abbreviations**: AUC, area under the curve; GMFR, geometric mean fold rise; GMT, geometric mean titer; IgG, immunoglobulin G; s.e.m., standard error of the mean; VZV, Varicella-Zoster Virus.

typically higher in females [30,31]. Consistent with this, our study identified significant post-vaccination differences in anti-gE IgG GMTs and GMFRs by sex and age. In line with prior evidence, females < 60 years in our cohort exhibited significantly higher GMTs and GMFRs compared to all other groups (males <60 years, males ≥60 years, and females ≥60 years).

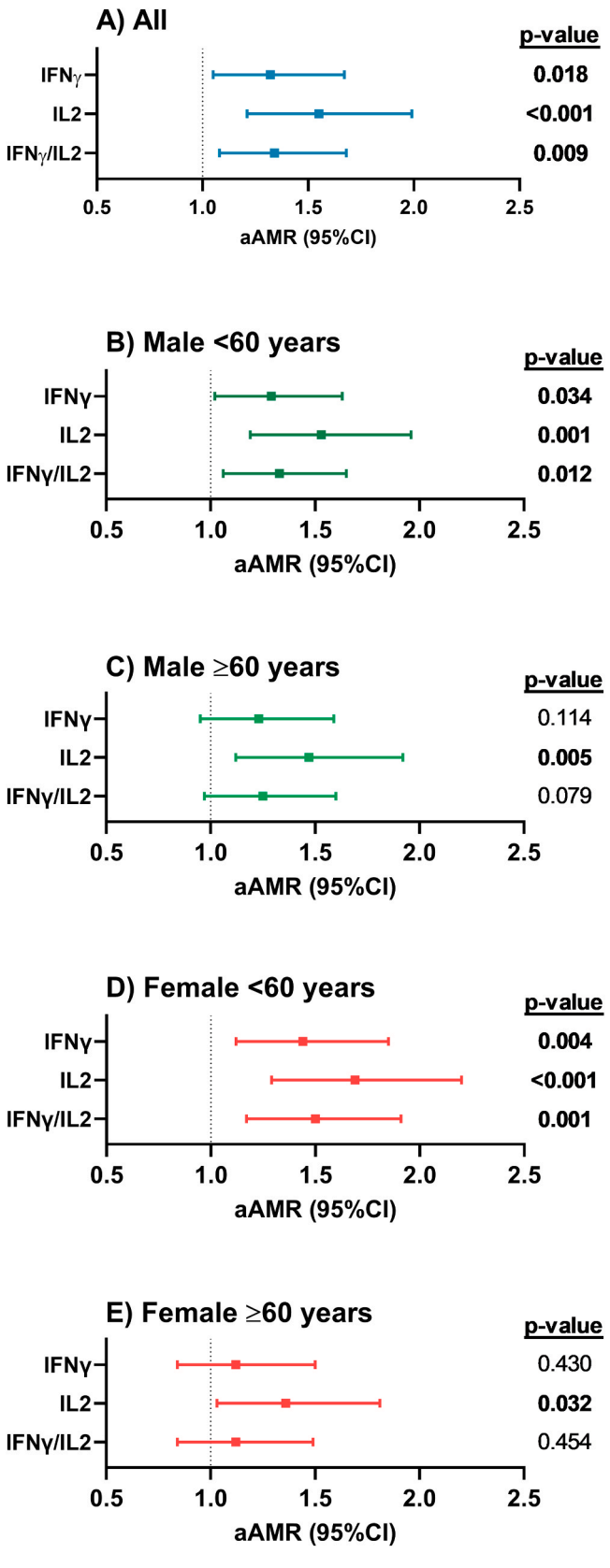
The sex-specific differences observed in our study are well-supported by the established role of sex hormones in modulating humoral immunity [32]. Estrogens, for instance, are known to enhance humoral responses by promoting B-cell proliferation and differentiation while skewing the immune system towards a Th2 profile that favors antibody production [30]. This hormonal influence offers a plausible explanation for two key findings in our cohort. Firstly, the natural decline in estrogen levels associated with menopause has been linked to diminished Th2 activity and, consequently, reduced antibody production [30,31], This provides a biological rationale for the attenuated responses we observed in women ≥ 60 years, an age group largely composed of post-menopausal individuals.

In parallel, androgens such as testosterone often exert immunomodulatory and relatively immunosuppressive effects, including the inhibition of B-lymphocyte proliferation [30]. This provides a biological basis for the frequently lower antibody titers seen in males compared to premenopausal women and likely contributes to the comparatively lower humoral responses observed in males < 60 years in our study. Taken together, the interplay between the immuno-enhancing effects of estrogen and the immunomodulatory effects of testosterone provides a strong biological rationale for the sex- and age-specific differences in vaccine immunogenicity reported both in the literature and in our cohort.

In contrast to the variability observed in humoral responses, robust VZV gE-specific CD4 + T-cell responses were induced across the cohort, as evidenced by high GMTs IFN-γ and IL-2 secretion rates (>99 %). This robust induction of T-cell immunity, which is critical for protection against herpes zoster [7], aligns with previous reports of high response rates in the general adult population [20]. Notably, and unlike the humoral response, the magnitude of these gE-specific CD4 + T-cell responses did not significantly differ by age or sex in our study. However, a non-significant trend towards higher T-cell responses was observed in individuals < 60 years, particularly among men. This observation resonates with studies reporting age-associated declines in VZV-specific cellular immunity, often attributed to immunosenescence [20,23,33]. Nonetheless, the literature remains heterogeneous, with other key studies demonstrating robust T-cell induction by RZV regardless of age [7,19,33]. Therefore, while our data hint at a potential influence of immunosenescence, the lack of a statistically significant effect underscores the complexity of RZV-induced T-cell immunity. Further investigation is warranted to fully elucidate the mechanisms underlying these age-related dynamics in older PLWH.

A central finding of this study was the significant positive correlation between VZV-specific T-cell responses and the magnitude of the post-vaccination humoral response. This association, evident for IFN-γ, IL-2, and polyfunctional IFN-γ/IL-2-secreting T-cell populations, suggests a well-coordinated RZV-induced immune response where robust cellular immunity supports or reflects enhanced antibody production. When stratified by sex and age, this association was most pronounced and consistent in females < 60 years, who demonstrated significant associations across all three T-cell functional profiles. Conversely, the marked attenuation of this T-cell/B-cell association in older participants likely reflects the impact of immunosenescence. Age-related declines in the immune system are known to impair the function of key cellular players, such as T follicular helper (Tfh) cells, which are essential for providing help to B cells and driving robust, high-affinity antibody production in germinal centers [34,35]. A decline in Tfh cell functionality could therefore disrupt the coordinated dialogue between T and B cells, leading to the diminished association between cellular and humoral responses observed in our older subgroups.

Therefore, our findings highlight that while RZV effectively promotes T- and B-cell association, host factors such as age and sex critically modulate the nature and strength of this coordinated response. These variations could, in turn, influence the long-term durability and protective efficacy of the vaccine across different patient subgroups. This



(caption on next column)

Fig. 2. Association of VZV-specific T-cell responses with the post-vaccination humoral response. Forest plots illustrate the association between post-vaccination VZV gE-specific T-cell responses (secreting IFN-γ, IL-2, or both) and the magnitude of the VZV-specific IgG response. Each plot displays the adjusted arithmetic mean ratio (aAMR) and its 95 % confidence interval (CI). The aAMR represents the multiplicative change in IgG levels for each one-unit increase in the ln-transformed T-cell response. Analyses are presented for (A) the entire cohort and stratified by sex and age: (B) males < 60 years, (C) males ≥ 60 years, (D) females < 60 years, and (E) females ≥ 60 years. **Statistics**: The association was modeled using generalized linear models (gamma family, log link) adjusted for pre-defined covariates (baseline CD4 + T-cell count, time on ART, HIV transmission route, and prior AIDS diagnosis). The resulting aAMRs and their 95 % CIs were derived using a non-parametric bootstrap (1000 replicates, BCa method). P-values for the association are shown for each T-cell subset. **Abbreviations**: aAMR, Adjusted Arithmetic Mean Ratio; CI, Confidence Interval; gE, Glycoprotein E; IFN-γ, Interferon-gamma; IL-2, Interleukin-2; VZV, Varicella-Zoster Virus.

suggests that while most individuals likely achieve protection, the quality and persistence of this immunity might differ—a critical consideration for optimizing long-term vaccination strategies in PLWH.

These findings underscore the need for ongoing evaluation of RZV immunogenicity in PLWH and support the routine inclusion of age and sex stratification in future vaccine studies. A deeper understanding of the factors that modulate both the magnitude and quality of humoral and cellular immunity—and their interplay—is essential. This knowledge will be critical for predicting long-term vaccine efficacy and for optimizing vaccination strategies to ensure maximal protection in this vulnerable population [7]. This is particularly relevant in PLWH, where identifying robust immune correlates of protection and understanding the influence of host-specific modulatory factors are key priorities for improving vaccine effectiveness [36–38].

4.1. Limitations

This study has several limitations that should be acknowledged. First, as a single-center study conducted in Madrid, Spain, the generalizability of our findings to PLWH populations with different geographical or ethnic backgrounds may be limited. Second, the absence of an HIV-negative control group precluded direct comparisons of vaccine immunogenicity with the general population. Third, our study design focused on PLWH with well-controlled HIV on effective ART, meaning all participants had undetectable viral loads; consequently, the impact of HIV viremia on vaccine response could not be assessed. Similarly, while nadir and baseline CD4 + T-cell counts were included as covariates, their potential impact might have been attenuated, as most participants exhibited robust CD4 + T-cell recovery (e.g., values predominantly above 500 cells/μL at baseline). Fourth, although we adjusted for several important clinical covariates, the observational nature of the study cannot entirely rule out residual confounding from unmeasured variables. Fifth, the sample sizes within certain sex and age strata—particularly for females ≥ 60 years—were relatively small, potentially limiting the statistical power to detect more subtle differences or associations in this subgroup. Sixth, the relatively short follow-up period did not allow for an evaluation of the long-term durability of the vaccine-induced immune responses in this population, an important consideration for immunocompromised individuals. Finally, our study did not collect data on other potentially relevant factors, such as CD8 T-cell counts, the CD4/CD8 ratio, BMI, or specific comorbidities (e.g., diabetes, renal insufficiency). Consequently, the potential influence of these variables on the observed vaccine responses could not be assessed in our analysis

5. Conclusions

In conclusion, RZV vaccination effectively induced both robust

humoral and T-cell responses, including IFN-γ and IL-2 secreting cells, in PLWH on effective ART. However, this response was critically modulated by age and sex. Females < 60 years demonstrated not only a superior humoral response but also the strongest association between T-cell activation and antibody production. To our knowledge, this is the first study in PLWH to evaluate RZV immunogenicity with a focus on sex- and age-based differences, highlighting important variability in vaccine responsiveness.

List of abbreviations

aAMR	Adjusted Arithmetic Mean Ratio
AIDS	Acquired Immunodeficiency Syndrome
AMR	Arithmetic Mean Ratio
ART	Antiretroviral Therapy
AUC	Area Under the Curve
BCa	Bias-Corrected and Accelerated
CI	Confidence Interval
gE	Glycoprotein E
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HGUGM	Hospital General Universitario Gregorio Marañón
HIV	Human Immunodeficiency Virus
HZ	Herpes Zoster
IDU	Intravenous Drug Use
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL-2	Interleukin-2
PBMC	Peripheral Blood Mononuclear Cell
PLWH	People Living with HIV
RZV	Recombinant Zoster Vaccine
s.e.m.	Standard Error of the Mean
SFC	Spot-Forming Cell
VZV	Varicella-Zoster Virus

CRediT authorship contribution statement

Isabel Gutiérrez: Data curation. **Cristina Díez:** Writing – review & editing, Project administration, Data curation, Conceptualization. **Juan Carlos López:** Data curation. **Leire Pérez-Latorre:** Data curation. **Daniel Sepúlveda-Crespo:** Investigation. **Francisco Tejerina:** Data curation. **Marchan Carrasco Ana:** Investigation. **Teresa Aldámiz-Echevarría:** Data curation. **Aurora Gómez-Tórtola:** Data curation. **Chiara Fanciulli:** Data curation. **Pita-Martínez Carlos:** Writing – review & editing, Validation, Resources, Investigation, Formal analysis. **Isidoro Martínez:** Writing – original draft, Validation, Methodology. **Salvador Resino:** Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization. **Marta Quero-Delgado:** Writing – review & editing, Validation, Investigation.

Patient consent statement

Patients were included after providing written informed consent.

Ethics approval statement

The study protocol and informed consent form were approved by the HGUGM Ethics Committee (Ref: MICRO.HGUGM.2023-08), and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Funding

This study was supported by grants from Agencia Estatal de Investigación [PID2024-157358OB-C21 to SR]. The study was also funded by the CIBER -Consorcio Centro de Investigación Biomédica en Red- (CB 2021), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, and Unión Europea – NextGenerationEU (CB21/13/00044). DSC is a 'Miguel Servet' researcher from ISCIII (grant #CP23CIII/00004).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Salvador Resino reports financial support was provided by Instituto de Salud Carlos III. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge using AI tools such as Gemini 2.5 Pro in Google AI Studio to assist with statistical analysis and language editing, grammar, and text flow. These tools were used under strict authorial control and supervision to refine the manuscript's presentation and did not contribute to the intellectual content.

We are grateful to all the participants, medical and nursery staff, and data managers who participated in this project. Their collaboration was instrumental in making this study possible. We also acknowledge the HIV BioBank, which was integrated into the Spanish AIDS Research Network and collaborating centers for providing the valuable clinical samples utilized in this research. The HIV BioBank, part of the Spanish AIDS Research Network, receives partial funding from the RD16/0025/0019 project within the Plan Nacional R+D+I, co-financed by ISCIII-FEDER.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2025.118663.

Data availability

Data will be made available on request.

References

[1] A.A. Gershon, J. Breuer, J.I. Cohen, R.J. Cohrs, M.D. Gershon, D. Gilden, C. Grose, S. Hambleton, P.G. Kennedy, M.N. Oxman, J.F. Seward, K. Yamanishi, Varicella zoster virus infection, Nat. Rev. Dis. Prim. 1 (2015) 15016.
[2] A.R. John, D.H. Canaday, Herpes zoster in the older adult, Infect. Dis. Clin. North Am. 31 (4) (2017) 811–826.
[3] K.J. Laing, W.J.D. Ouwendijk, D.M. Koelle, G. Verjans, Immunobiology of Varicella-Zoster virus infection, J. Infect. Dis. 218 (_2) (2018) S68–S74.
[4] M.A. Hakami, F.R. Khan, O. Abdulaziz, K. Alshaghdali, A. Hazazi, A.F. Aleissi, A. Abalkhail, B.S. Alotaibi, A.Y.M. Alhazmi, N. Kukreti, A.S. Binshaya, Varicella-zoster virus-related neurological complications: from infection to immunomodulatory therapies, Rev. Med. Virol. 34 (4) (2024) e2554.
[5] M.J. Levin, A. Weinberg, Immune responses to zoster vaccines, Hum. Vaccin Immunother. 15 (4) (2019) 772–777.
[6] T.C. Anderson, N.B. Masters, A. Guo, L. Shepersky, A.J. Leidner, G.M. Lee, C. N. Kotton, K.L. Dooling, Use of recombinant zoster vaccine in immunocompromised adults aged >/=19 years: recommendations of the advisory committee on immunization practices - United States, 2022, MMWR Morb. Mortal. Wkly Rep. 71 (3) (2022) 80–84.
[7] L. Losa, I.C. Antonazzo, G. Di Martino, G. Mazzaglia, S. Tafuri, L.G. Mantovani, P. Ferrara, Immunogenicity of recombinant zoster vaccine: a systematic review, Meta-Analysis, and Meta-Regression, Vaccines 12 (5) (2024).
[8] Y. Xia, X. Zhang, L. Zhang, C. Fu, Efficacy, effectiveness, and safety of herpes zoster vaccine in the immunocompetent and immunocompromised subjects: a systematic review and network meta-analysis, Front. Immunol. 13 (2022) 978203.
[9] C.W. Cai, I. Sereti, Residual immune dysfunction under antiretroviral therapy, Semin Immunol. 51 (2021) 101471.
[10] Y.Y. Syed, Recombinant zoster vaccine (Shingrix((R))): a review in herpes zoster, Drugs Aging 35 (12) (2018) 1031–1040.
[11] S.L. McKay, A. Guo, S.A. Pergam, K. Dooling, Herpes zoster risk in immunocompromised adults in the United States: a systematic review, Clin. Infect. Dis. 71 (7) (2020) e125–e134.

[12] F. Marra, K. Parhar, B. Huang, N. Vadlamudi, Risk factors for herpes zoster infection: a meta-analysis, Open Forum Infect. Dis. 7 (1) (2020) ofaa005.
[13] M. Hentzien, F. Bonnet, E. Bernasconi, E. Biver, D.L. Braun, A. Munting, K. Leuzinger, O. Leleux, S. Musardo, V. Prendki, P. Schmid, C. Staehelin, M. Stoeckle, C.S. Walti, L. Wittkop, V. Appay, A.M. Didierlaurent, A. Calmy, Immune response to the recombinant herpes zoster vaccine in people living with HIV over 50 years of age compared to non-HIV age-/gender-matched controls (SHINGR'HIV): a multicenter, international, non-randomized clinical trial study protocol, BMC Infect. Dis. 24 (1) (2024) 329.
[14] V. Carta, L. Mangeri, G. Tiecco, E. Focà, E. Quiros-Roldan, M.A. De Francesco, Immunogenicity and safety of live attenuated and recombinant/inactivated varicella zoster vaccines in people living with HIV: a systematic review, Hum. Vaccin Immunother. 20 (1) (2024) 2341456.
[15] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inf. 42 (2) (2009) 377–381.
[16] M.J. Munoz-Gomez, P. Ryan, M. Quero-Delgado, M. Martin-Vicente, G. Cuevas, J. Valencia, E. Jimenez, N. Blanca-Lopez, M.A. Lara-Alvarez, J.A. Hernandez-Rivas, G. Redondo, V. Mas, D. Sepulveda-Crespo, M. Vazquez, J. Torres-Macho, I. Martinez, S. Resino, Immune response against the SARS-CoV-2 spike protein in cancer patients after COVID-19 vaccination during the omicron wave: a prospective study, J. Infect. Public Health 17 (7) (2024) 102473.
[17] C.-A. Siegrist, 2 - vaccine immunology, in: S.A. Plotkin, W.A. Orenstein, P.A. Offit, K.M. Edwards (Eds.), Plotkin's Vaccines, Seventh ed., Elsevier, 2018, pp. 16–34, e7.
[18] H. Lal, A.L. Cunningham, O. Godeaux, R. Chlibek, J. Diez-Domingo, S.J. Hwang, M. J. Levin, J.E. McElhaney, A. Poder, J. Puig-Barbera, T. Vesikari, D. Watanabe, L. Weckx, T. Zahaf, T.C. Heineman, Z.O.E.S. Group, Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults, N. Engl. J. Med 372 (22) (2015) 2087–2096.
[19] A. Strezova, J. Diez-Domingo, K.Al Shawafi, J.C. Tinoco, M. Shi, P. Pirrotta, A. Mwakingwe-Omari, G. Zoster-049 Study, Long-term protection against herpes zoster by the adjuvanted recombinant zoster vaccine: interim efficacy, immunogenicity, and safety results up to 10 years after initial vaccination, Open Forum Infect. Dis. 9 (10) (2022) ofac485.
[20] A.L. Cunningham, T.C. Heineman, H. Lal, O. Godeaux, R. Chlibek, S.J. Hwang, J. E. McElhaney, T. Vesikari, C. Andrews, W.S. Choi, M. Esen, H. Ikematsu, M. K. Choma, K. Pauksens, S. Ravault, B. Salaun, T.F. Schwarz, J. Smetana, C. V. Abeele, P. Van den Steen, I. Vastiau, L.Y. Weckx, M.J. Levin, Z.O.E.S. Group, Immune responses to a recombinant glycoprotein e herpes zoster vaccine in adults aged 50 years or older, J. Infect. Dis. 217 (11) (2018) 1750–1760.
[21] K.J. Laing, E.S. Ford, M.J. Johnson, M.J. Levin, D.M. Koelle, A. Weinberg, Recruitment of naive CD4+ t cells by the recombinant zoster vaccine correlates with persistent immunity, J. Clin. Invest 133 (23) (2023).
[22] L.J. Blank, M.J. Polydefkis, R.D. Moore, K.A. Gebo, Herpes zoster among persons living with HIV in the current antiretroviral therapy era, J. Acquir Immune Defic. Syndr. 61 (2) (2012) 203–207.
[23] A. Weinberg, J.H. Zhang, M.N. Oxman, G.R. Johnson, A.R. Hayward, M. J. Caulfield, M.R. Irwin, J. Clair, J.G. Smith, H. Stanley, R.D. Marchese, R. Harbecke, H.M. Williams, I.S.F. Chan, R.D. Arbeit, A.A. Gershon, F. Schödel, V. A. Morrison, C.A. Kauffman, S.E. Straus, K.E. Schmader, L.E. Davis, M.J. Levin, US Department of Veterans Affairs (VA) Cooperative Studies Program Shingles Prevention Study Investigators, Varicella-Zoster Virus–Specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine, J. Infect. Dis. 200 (7) (2009) 1068–1077.
[24] S.Y. Park, M.J. Levin, J. Canniff, M. Johnson, D.S. Schmid, A. Weinberg, Development of antibody-dependent cellular cytotoxicity in response to recombinant and live-attenuated herpes zoster vaccines, NPJ Vaccin. 7 (1) (2022) 123.
[25] E. Muchtar, A.B. Koehler, M.J. Johnson, K.G. Rabe, W. Ding, T.G. Call, J.F. Leis, S. S. Kenderian, S.R. Hayman, Y. Wang, P.J. Hampel, M.A. Holets, H.C. Darby, S. L. Slager, N.E. Kay, C. Miao, J. Canniff, J.A. Whitaker, M.J. Levin, D.S. Schmid, R. B. Kennedy, A. Weinberg, S.A. Parikh, Humoral and cellular immune responses to recombinant herpes zoster vaccine in patients with chronic lymphocytic leukemia and monoclonal b cell lymphocytosis, Am. J. Hematol. 97 (1) (2022) 90–98.
[26] M. Koldehoff, P.A. Horn, M. Lindemann, Cellular immune response after vaccination with an adjuvanted, recombinant zoster vaccine in allogeneic hematopoietic stem cell transplant recipients, Vaccines 10 (5) (2022).
[27] E.M. Berkowitz, G. Moyle, H.J. Stellbrink, D. Schurmann, S. Kegg, M. Stoll, M. El Idrissi, L. Oostvogels, T.C. Heineman, H.Zs.S.G. Zoster, Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study, J. Infect. Dis. 211 (8) (2015) 1279–1287.
[28] C. Boutry, A. Hastie, J. Diez-Domingo, J.C. Tinoco, C.J. Yu, C. Andrews, J. Beytout, C. Caso, H.S. Cheng, H.J. Cheong, E.J. Choo, D. Curiac, E. Di Paolo, M. Dionne, T. Eckermann, M. Esen, M. Ferguson, W. Ghesquiere, S.J. Hwang, T.J. Avelino-Silva, P. Kosina, C.S. Liu, J. Markkula, B. Moeckesch, C. Murta de Oliveira, D. W. Park, K. Pauksens, P. Pirrotta, G. Plassmann, C. Pretswell, L. Rombo, B. Salaun, J. Sanmartin Berglund, I. Schenkenberger, T. Schwarz, M. Shi, B. Ukkonen, T. Zahaf, C. Zerbini, A. Schuind, A.L. Cunningham, G. Zoster-049 Study, The adjuvanted recombinant zoster vaccine confers Long-Term protection against herpes zoster: interim results of an extension study of the pivotal phase 3 clinical trials ZOE-50 and ZOE-70, Clin. Infect. Dis. 74 (8) (2022) 1459–1467.
[29] A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, C.V. Abeele, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, Fd Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S. A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, T.C. Heineman, Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older, N. Engl. J. Med. 375 (11) (2016) 1019–1032.
[30] E.N. Fish, The X-files in immunity: sex-based differences predispose immune responses, Nat. Rev. Immunol. 8 (9) (2008) 737–744.
[31] I.F. Cook, Sexual dimorphism of humoral immunity with human vaccines, Vaccine 26 (29-30) (2008) 3551–3555.
[32] S.L. Klein, A. Jedlicka, A. Pekosz, The xs and y of immune responses to viral vaccines, LANCET Infect. Dis. 10 (5) (2010) 11.
[33] T.F. Schwarz, S. Volpe, G. Catteau, R. Chlibek, M.P. David, J.H. Richardus, H. Lal, L. Oostvogels, K. Pauksens, S. Ravault, L. Rombo, G. Sonder, J. Smetana, T. Heineman, A. Bastidas, Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults, Hum. Vaccin Immunother. 14 (6) (2018) 1370–1377.
[34] G. Varricchi, L. Bencivenga, R. Poto, A. Pecoraro, M.H. Shamji, G. Rengo, The emerging role of t follicular helper (T(FH)) cells in aging: influence on the immune frailty, Ageing Res. Rev. 61 (2020) 101071.
[35] S. Dave, A. Ballesteros-Tato, Noncanonical functions of t follicular helper cells, Sci. Immunol. 10 (108) (2025) eadr1052.
[36] S. Kerneis, O. Launay, C. Turbelin, F. Batteux, T. Hanslik, P.Y. Boelle, Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis, Clin. Infect. Dis. 58 (8) (2014) 1130–1139.
[37] G. Montesi, M. Augello, J. Polvere, G. Marchetti, D. Medaglini, A. Ciabattini, Predicting humoral responses to primary and booster SARS-CoV-2 mRNA vaccination in people living with HIV: a machine learning approach, J. Transl. Med. 22 (1) (2024) 432.
[38] A. Antinori, S. Cicalini, S. Meschi, V. Bordoni, P. Lorenzini, A. Vergori, S. Lanini, L. De Pascale, G. Matusali, D. Mariotti, A. Cozzi Lepri, P. Galli, C. Pinnetti, R. Gagliardini, V. Mazzotta, I. Mastrorosa, S. Grisetti, F. Colavita, E. Cimini, E. Grilli, R. Bellagamba, D. Lapa, A. Sacchi, A. Marani, C. Cerini, C. Candela, M. Fusto, V. Puro, C. Castilletti, C. Agrati, E. Girardi, F. Vaia, H.-V.S. Group, Humoral and cellular immune response elicited by mRNA vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people living with human immunodeficiency virus receiving antiretroviral therapy based on current CD4 T-Lymphocyte count, Clin. Infect. Dis. 75 (1) (2022) e552–e563.