AIDS Research and Therapy

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Serological status of measles, mumps, and rubella antibodies in HIV-positive women of childbearing age at a referral hospital in Iran

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Abstract

Background The human immunodeficiency virus (HIV) increases susceptibility to measles, mumps, and rubella (MMR) infections due to decreased cluster of differentiation 4 + T-cell levels and rapid waning of protective antibodies following vaccination, which imposes a significant impact on HIV-positive women of reproductive age, for whom MMR vaccination is a crucial preventive measure. This study aimed to shed light on the immunity status of women of childbearing age with HIV infection post-MMR-vaccination during their childhood and the necessity of further vaccination in these individuals.

Methods To evaluate seroconversion rates following vaccination through Iran's NIP or previous infection by assessing MMR IgG levels, all Iranian women aged 18–45 years referred to our voluntary counseling center, with or without HIV infection and CD4 levels 200 cells/mm^3 or higher at the time of enrollment, were invited to participate. Data were collected through the Hospital Information System and questionnaires, and blood samples were taken to evaluate the seroconversion following MMR vaccination via NIP or previous MMR infection.

Results In this study, 150 women participated, with a mean age (± SD) of 36.49 (± 6.80). Mean rubella and measles IgG levels of HIV-positive participants (95.08 ± 79.42 IU/MI) were higher than HIV-negative peers (8.98 ± 3.83 mg/dL) with no significant associations (p-value > 0.05). However, mumps IgG levels were significantly lower compared to HIV-negative participants (9.87 ± 28.70 mg/dL, p-value < 0.001). Additionally, HIV-positive participants significantly exhibited lower total immunity (*n* = 73, 97.3) compared to HIV-negative participants (*n* = 64, 85.3) (p-value = 0.07). HIV-positive individuals who did not have seroimmunity against mumps infection had significantly lower CD4 NADIR counts (cells/mm3) (mean ± SD = 259.00 ± 203.31, p-value: 0.025). Moreover, regression analyses demonstrated significant associations between decreased mumps IgG levels and lower CD4 NADIR counts (AOR = 1.004, 95% CI = 1-1.008, p value = 0.03).

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Conclusion Our research found that HIV-positive women may need MMR revaccination due to increased susceptibility to at least one of these viruses. We also highlighted the significance of considering lower CD4 NADIR as a risk factor for mumps development in women living with HIV infection.

Keywords Measles, Mumps, Rubella, MMR, MMR vaccination, HIV, Seronegativity, Women of childbearing age

Introduction

Human immunodeficiency virus (HIV) increases the susceptibility of affected individuals to vaccine-preventable infections, including measles, mumps, and rubella (MMR), due to a decrease in the cluster of differentiation 4+ (CD4+) T-cells and exhaustion of immune system as a result of and chronic immune activation, even in cases of early antiretroviral therapy (ART) initiation, which causes significant global morbidity and mortality burdens, particularly among low socio-economic populations [1–5] [6, 7]. Women of childbearing age with HIV face a multitude of complications, including a variety of congenital disabilities and anomalies, miscarriages, fetal death, pneumonia, hepatitis, keratoconjunctivitis, otitis media, and aseptic meningitis [8–12]. Since the introduction of ART, life expectancy has increased in this vulnerable population as CD4 + T-cell and B-cell counts increase, resulting in a more promising response to vaccination and infections [13, 14].

Routine vaccination is recommended for people living with HIV (PLWH), including inactivated vaccines like COVID-19, hepatitis A, hepatitis B, human papillomavirus (HPV), inactivated influenza, meningococcal, pneumococcal, tetanus, diphtheria, pertussis, and zoster. Recently, live attenuated vaccine administration in PLWH with CD4 + T-cell counts ≥ 200 cells/mm^3 has been recommended [15–22].In Iran, the measles vaccination program began in 1984, with all infants vaccinated by 2003. Rubella vaccination was added to the National Immunization Program (NIP) in 2003–2004, providing adults under 25 with a booster and a follow-up dose a month later. Mumps vaccination was introduced in 2004, and since then, the MMR vaccine has been administered to all infants [24, 25]; as a result, Iran achieved a measles elimination certificate in the Eastern Mediterranean region alongside rubella elimination [26]. Despite over 95% vaccination coverage among children [27], delayed and age-inappropriate MMR vaccination, along with low refugee participation in the free NIP over the past decade, have contributed to sporadic measles outbreaks [28–34], as in 2022, 214 measles cases were reported, half involving foreigners [35].

Nokhodian et al. reported a lack of MMR antibodies following previous vaccination during their participants' childhood or infancy in 34.2%, 22.8%, and 19.9% of their participants [23]. Additionally, Keshavarz et al. reported that 20.8%, 35.84%, and 3.7% of their participants had nonprotective levels of measles, mumps, and rubella antibodies years after MR or MMR vaccination during childhood and infancy [24]. One study also reported seropositivity rates of 76.2%, 89.3%, and 76.9% for measles, mumps, and rubella, respectively, following a mass vaccination campaign in 2003 [25].

The majority of women living with HIV (WLWH) are vaccinated during their childhood, and seroconversion occurs in healthy women long before being diagnosed with HIV. WLWH often experience the waning of antibodies after HIV infection onset, which is later paused following ART administration [26, 27]. Studies on other nationalities reported suboptimal seroconversion rates ranging from 25 to 72% compared to over 90% for vaccine response in healthy children and observed rapid waning of MMR antibodies post-vaccination [28–32]. One study also reported a seronegativity rate of 34.5% after vaccination in perinatal HIV-positive women of childbearing age [33].

Limited data exist on MMR seroprevalence among Iranian WLWH, particularly women of childbearing age, despite the high risk of life-threatening complications. To address this gap, we conducted a case-control study to evaluate serological levels of MMR antibodies in WLWH at a tertiary hospital in Tehran, Iran. We hypothesized that WLWH lack protective antibodies compared to healthy individuals, highlighting the need for targeted vaccination strategies in this vulnerable population.

Methods

Study design and participants

A case-control study evaluating the serological levels of MMR antibodies following infection or previous vaccination through NIP was conducted at the voluntary counseling and testing (VCT) Center at Imam Khomeini Hospital Complex in Tehran, Iran.

Between March 2023 and 2024, all WLWH between the ages of 18–45 years referred to the VCT Center, with or without previous HIV-proven infection (positive enzyme-linked immunosorbent assay, ELISA, and Western blot results), were invited to participate. The information about the program and data collection was orally discussed with every willing participant. Cases were defined as Iranian HIV-positive women aged between 18 and 45 years old with CD4 counts greater than 200 cells/mm^3. Additionally, controls included Iranian HIV-negative women between the ages of 18 and 45 years old. Details regarding subject selection are demonstrated in Fig. 1.

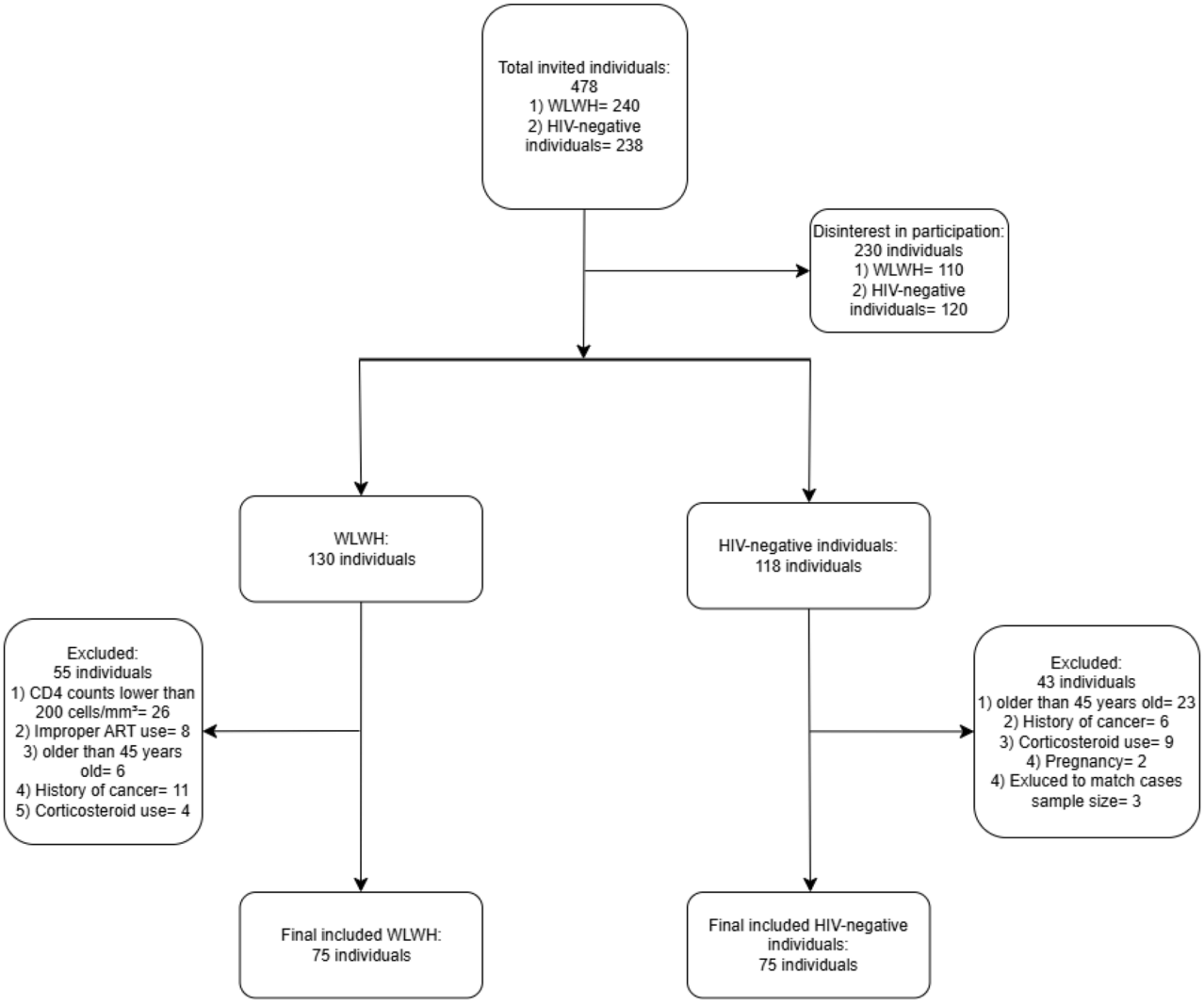

Fig. 1 Flowchart of study participant selection process

The sample size for the study was calculated using G*Power 3.1 software based on the T-tests and the difference between two independent means and, a priori analysis was conducted to determine the required sample size. The input parameters were effect size (0.495), error probability (0.05), power (1–β error probability of 0.85), and allocation ratio (N2/N1 of 1). The output parameters included noncentrality parameter δ of 3.0312436, critical t-value of 1.9761225, degrees of freedom (Df) of 148, sample size for groups 1 and 2 of 75, each, which resulted in a total sample size of 150, and an actual power of 0.8534979.

Subject selection

The inclusion criteria were all native Iranian WLWH between the ages of 18 and 45 years, with CD4 levels of 200 cells/mm^3 or higher at the study time, under proper ART. The HIV-negative population was chosen through a comprehensive questionnaire on risk factors and previous possible exposures to HIV and any previous testing that was available within the Hospital Information System (HIS). The exclusion criteria were age younger than 18 years or older than 45 years, disinterest in participation, CD4 levels lower than 200 cells/mm^3, improper ART since HIV diagnosis was established, past medical history of immunosuppression other than HIV, including cancer or corticosteroid use and chemotherapy, and pregnancy.

Measurements and tools

In the WLWH, information including age, first CD4 levels upon HIV diagnosis, most recent CD4 levels, CD4 NADIR, HIV diagnosis duration, history of previous MMR vaccination, and previous history of MMR infection were collected. In healthy participants, age, and previous history of MMR infection were retrieved through

Table 1 Demographic and clinical characteristics of study population

Characteristics	Total population (*n* = 150)	WLWH [a] (*n* = 75)	Non-WLWH (*n* = 75)	*P*-value
Age (years), mean ± SD [a]	36.49 ± 6.80	37.76 ± 5.95	35.15 ± 7.4	**0.021**
Measles IgG [*a] (mg/dL), mean ± SD	8.79 ± 4.55	8.98 ± 3.83	8.60 ± 5.18	0.61
Rubella IgG (IU/mL), mean ± SD	82.98 ± 72.30	95.08 ± 79.42	70.87 ± 62.61	0.26
Mumps IgG (mg/dL), mean ± SD	10.73 ± 20.76	9.87 ± 28.70	11.58 ± 6.56	**< 0.001**
Previous measles*, n (%)	27 (20.9)	11 (20.4)	16 (21.3)	0.89
Previous rubella*, n (%)	6 (4.7)	3 (5.6)	3 (4)	0.68
Previous mumps*, n (%)	24 (18.6)	11 (20.4)	13 (17.3)	0.66
MMR [a] vaccination, n (%)	7 (4.8)	3 (4)	4 (5.6)	0.713

*Missing data for 21 patients; [a] WLWH: women living with HIV; SD: Standard deviation; MMR: Mumps, Measles, Rubella; IgG: Immunoglobulin G

an epidemiological and clinical questionnaire and the HIS.

After the initial data were collected, blood samples were obtained from both WLWH and healthy participants. A total of 6 mL of blood was taken, with 2 mL collected for each mumps, rubella, and measles test. The samples were analyzed to detect antibodies. For measles and rubella IgG, PishtazTeb indirect ELISA kit and Mumps IgG Vircell indirect immunoassay kit were utilized. (Sensitivity = 100%, specificity = 100%) According to the manufacturer's instructions, a rubella IgG concentration greater than 11 IU/mL and a mumps and measles IgG concentration greater than 11 mg/dL index were considered to reflect seroimmunity Therefore, participants with rubella IgG values greater than 11 IU/mL and mumps and measles IgG values greater than 11 mg/dL were considered seroimmune. Subsequently, the results were recorded in an Excel sheet and compared between the two groups.

Ethical considerations

Informed written consent was provided to each participant as well as orally explained. The Research Ethics Committee of Tehran University of Medical Sciences (TUMS) approved this study, and patient confidentiality was maintained by coding.

Statistical analysis

SPSS (Version 26.0, IBM Corp., Armonk, NY, USA) and R (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria) software were utilized to analyze the data. Quantitative variables were expressed as the mean, standard deviation (SD), and interquartile range (IQR), and qualitative variables were reported as absolute frequencies and percentages.

Continuous data were checked for normality using the Kolmogorov-Smirnov test, and students' T-tests were used for parametric and Mann-Whitney U tests were used for non-parametric variables. The Chi-square and Fisher's exact tests compared frequencies between immune and non-immune patients. Univariate binary logistic regression analysis was performed to predict Mumps and rubella immunity using age and CD4 NADIR. To perform the sensitivity analysis, missing values were handled using the K-nearest neighbor (KNN) algorithm (k = 5) for independent variables (age and CD4 NADIR) [34]. Sensitivity analysis was then performed using multivariate binary logistic regression analysis (dependent variable: mumps immunity, independent variables: age and CD4 NADIR). Multivariate binary logistic regression was then performed considering age and CD4 NADIR as independent variables to determine their combined effect on immunity, accounting for potential confounding factors. A p-value less than 0.05 was considered significant.

Results

Initially, 478 individuals, including 240 WLWH and 238 HIV-negative participants, were invited to participate, of whom 130 WLWH and 118 HIV-negative individuals agreed upon. After evaluating participants for inclusion criteria fulfillment, 75 WLWH (cases) and 75 HIV-negative participants (controls) were enrolled (Fig. 1).

In total, 150 women of childbearing age were enrolled, and their MMR IgG levels were evaluated. The study population included 75 WLWH with a mean age (± SD) of 37.76 ± 5.95 years and 75 HIV-negative participants with a mean age (± SD) of 35.15 ± 7.4 years, with WLWH significantly older than those in the HIV-negative population (p value: 0.021). The characteristics of the 21 participants with missing values are discussed in Additional File 1.

Among the study population, 20.9% reported a previous history of measles, 4.7% reported a prior history of rubella, and 18.6% reported a previous mumps infection. The mean mumps protective antibody levels were significantly greater in HIV-negative individuals despite the greater number of previous mumps infection reports among WLWH (mean ± SD = 11.58 ± 6.56, p-value < 0.001). Regarding MMR vaccination, there were no significant differences between HIV-positive and negative individuals (p-value = 0.713).

Table 2 depicts the associations between age, HIV status, and both groups' MMR immunity. This investigation revealed no significant relation between measles

Table 2 The association between immunity, HIV status and age

	Immunity status	Age (year) Mean ± SD*	*P*-value	WLWH* (*n* = 75) *n* (%)	Non-WLWH (*n* = 75) *n* (%)	*P*-value
Measles	Immune	37.69 ± 6.89	0.134	30 (40.0)	21 (28.0)	0.168
	Non-immune	35.89 ± 6.7		45 (60.0)	54 (72.0)	
Rubella	Immune	36.82 ± 6.48	0.253	62 (82.7)	67 (89.3)	0.347
	Non-immune	34.57 ± 8.32		13 (17.3)	8 (10.7)	
Mumps	Immune	37.07 ± 6.87	0.519	8 (10.7)	37 (49.3)	**< 0.001**
	Non-immune	36.26 ± 6.79		67 (89.3)	38 (50.7)	
Total seroimmunity	Immune	38.36 ± 5.56	0.344	2 (2.7)	11 (14.7)	**0.017**
	Non-immune	36.34 ± 6.88		73 (97.3)	64 (85.3)	

*SD: Standard deviation; WLWH: women living with HIV

Table 3 Characteristics of women living with HIV (WLWH) in a referral hospital in Tehran, Iran, March 2023–2024

		Mumps Mean ± SD*	Measles Mean ± SD	Rubella Mean ± SD	Total seroimmunity Mean ± SD
Age (years)	Immune	39.50 ± 3.62	38.57 ± 6.33	38.40 ± 5.29	39.00 ± 2.83
	Non-Immune	37.55 ± 6.16	37.22 ± 5.70	34.69 ± 7.98	37.73 ± 6.02
	P Value	0.385	0.341	**0.04**	0.767
First CD4*(cells/mm^3)	Immune	567.00 ± 196.79	434.57 ± 297.92	410.84 ± 290.96	682.00 ± 77.78
	Non-Immune	370.94 ± 284.46	363.38 ± 270.56	301.31 ± 222.30	383.90 ± 281.54
	P Value	0.063	0.287	0.205	0.141
Last CD4 (cells/mm^3)	Immune	731.88 ± 318.00	773.23 ± 360.99	735.15 ± 343.79	997.50 ± 60.10
	Non-Immune	717.73 ± 341.88	683.24 ± 319.76	643.38 ± 305.95	711.62 ± 338.72
	P Value	0.917	0.261	0.793	0.240
CD4 NADIR (cells/mm^3)	Immune	450.57 ± 268.68	311.07 ± 211.58	296.27 ± 218.83	429.00
	Non-Immune	259.00 ± 203.31	255.07 ± 218.37	193.00 ± 186.98	275.49 ± 216.71
	P Value	0.025	0.284	0.119	0.484
HIV* duration (years)	**Immune**	3039.25 ± 2390.46	3235.31 ± 1779.80	2908.98 ± 1910.48	4940.50 ± 2595.79
	Non-Immune	2963.52 ± 1873.80	2801.82 ± 2001.46	3266.00 ± 1997.98	2917.01 ± 1889.78
	P Value	0.917	0.346	0.546	0.142

*SD: Standard deviation; CD4: Cluster of differentiation 4; HIV: Human immunodeficiency virus

Table 4 Comparison of multivariate logistic regression analyses results before and after KNN imputation

		Before KNN* imputation			After KNN imputation		
		AOR*[a]	95% CI* Lower bound-Upper bound	P-value	AOR*[a]	95% CI Lower bound-Upper bound	P-value
Mumps immunity	CD4* NADIR (cells/mm^3)	1.004	1.000-1.008	**0.030**	1.006	1.006–1.021	**< 0.001**
	Age (year)	1.117	0.922–1.353	0.257	1.021	0.966–1.079	0.463

*AOR: adjusted odds ratio; KNN: K-nearest neighbor; CI: Confidence interval; CD4: Cluster of differentiation 4; [a] Adjusted by age

and rubella immunity regarding HIV status and age. WLWH were more susceptible to mumps infection (p-value < 0.001), and total immunity was significantly lower in the WLWH group than in the non-WLWH group. Only 10.7% of the WLWH had seroimmunity to mumps, while 49.3% of the HIV-negative population were immune to mumps.

Table 3 describes the associations between immunity to MMR, total immunity, first and last CD4, CD4 NADIR, and HIV duration among WLWH. Older participants exhibited greater immunity in all four groups. However, only immunity to rubella and age were significant (P-value = 0.04). Moreover, significantly lower CD4 NADIR counts were observed among WLWH who did not have seroimmunity to mumps infection (P-value = 0.025).

A sensitivity analysis of age, CD4 NADIR, and mumps immunity variables (using missing data handling) was performed. Although there were slight increases in the adjusted odds ratio (AOR) and confidence interval values, the results remained stable throughout both analyses, demonstrating the robustness of our model (Table 4).

The results of Table 5 provide the logistic regression analysis predicting immunity to mumps and rubella using the significant variables previously discussed. Although older WLWH exhibited increased immunity

Table 5 Univariate and multivariate regression analysis of mumps and Rubella immunity

		Univariate			Multivariate		
		OR*	95% CI Lower bound-Upper bound	P-value	AOR*[a]	95% CI Lower bound-Upper bound	P-value
Mumps seroimmunity	CD4* NADIR (cells/mm^3)	1.004	1.000-1.007	**0.037**	1.004	1.000-1.008	**0.030**
	Age (years)	1.072	0.917–1.253	0.382	1.117	0.922–1.353	0.257
Rubella seroimmunit	CD4* NADIR (cells/mm^3)	1.002	0.999–1.006	0.160	-	-	-
	Age (years)	1.095	0.999–1.201	0.052	-	-	-

*OR: Odds ratio; AOR: Adjusted odds ratio; CD4: Cluster of differentiation 4, [a] adjusted by age

to rubella in simple analysis, neither the CD4 NADIR (OR = 1.002, 95% CI = 0.999–1.006, P value > 0.05) nor age (OR = 1.095, 95% CI = 0.999–1.201, P value > 0.05) was significant in univariate analysis. However, the CD4 NADIR in both univariate (OR = 1.004, 95% CI = 1.000-1.007, P value = 0.037) and multivariate logistic regressions (AOR = 1.004, 95% CI = 1.000-1.008, P value = 0.030) was significant for mumps immunity, despite small effect sizes, indicating that CD4 NADIR may contribute to mumps immunity in a relatively small manner, as by every unit increase in CD4 NADIR, the odds of immunity to mumps may slightly increase. Moreover, regarding mumps seroimmunity, age did not reach statistical significance in both univariate (OR = 1.072, 95% CI = 0.917–1.253, P value > 0.05) and multivariate (AOR = 1.117, 95% CI = 0.922–1.353, P value > 0.05) analyses.

Discussion

This study found relatively low rates of seroimmunity tomumps among WLWH of childbearing age compared to the HIV-negative participants. This research also illustrated that participants with lower CD4 NADIR exhibited higher rates of mumps seronegativity than those with higher CD4 NADIR counts. Kerr et al., reported the same baseline results as our study; however, their study population exhibited seronegativity lower than the 89% reported in our investigation [35].

Llenas-García et al., evaluated the need for MMR vaccination in HIV-positive immigrants in Spain. The authors reported MMR susceptibilities of 53.1%, 24.7%, and 7.4%, respectively, among 81% of their study population, supporting our main finding of lower total immunity among WLWH. These results suggest that HIV, singularly, may be an indicator of MMR vaccination in PLWH and the need for routine screening tests for vaccine-preventable diseases in this already-affected population. In contrast with the study by Llenas-García et al., which reported younger age as a risk factor for measles infection in PLWH, we found no relation between the two variables. In addition, they did not find that the CD4 NADIR correlated with MMR infection [36]. Grabmeier-Pfistershammer et al., conducted a similar study to evaluate the percentage of individuals with MMR susceptibility among the Austrian HIV population. They found relatively high susceptibility rates to at least one MMR infection. This finding is consistent with our findings, where we found high rates of susceptibility to mumps infection among both WLWH and non-WLWH. Additionally, they found no relation between rubella and age and reported that older age was a protective factor against measles infection. Interestingly, they found that the CD4 NADIR correlated with immunity only against measles infection and reported no correlation between CD4 NADIR counts and mumps or rubella susceptibility. Similarly, they reported heterogeneous seropositivity rates between different pathogens, which was also observed in our study. However, we only found a significant relation between mumps and HIV status, and the other two pathogens exhibited no significant associations [37].

The high susceptibility to mumps infection in both populations could be due to the lack of immunization in nearly all of the study population since it was first introduced in 2004 and was only administered to infants during that year. Schwarze-Zander et al., reported a significant association between measles seropositivity and younger age, which is in contrast with the findings of Llenas-García and Grabmeier-Pfistershammer, who defined younger age as a risk factor for measles infection, and this study, in which the authors found no correlation between age and measles infection. These contradicting findings could result from different MMR immunization programs within different countries. However, a more thorough study is needed. They also reported that 35% of their population is susceptible to at least one vaccine-preventable disease caused by MMR, similar to previously mentioned studies. Following our investigation, where we reported a 17% rate of rubella seropositivity among WLWH, they reported a 9% rubella seronegativity rate among HIV positive women of childbearing age, emphasizing the importance of revaccination, considering the severe rubella infection complications during pregnancy [38].

We would like to acknowledge the limitations of the study. First, the previous history of MMR infection was based on participants' reports, which increases the recall bias in data gathering and might influence seronegativity. A similar issue was observed when collecting data on healthy individuals. We relied solely on subjective reports

and laboratory data within the HIS. Considering that a limited population might have affected our results, we suggest further studies with larger populations. Because most of our population did not receive MMR vaccination in terms of a one united vaccine, more studies are needed to determine the precise effect of MMR vaccination on the immunity of women of childbearing age and the need to revaccinate in this population. We propose further studies with more diverse populations, including different nationalities, immigrants, and larger populations, to determine the need for MMR vaccination among PLWH in Iran. Furthermore, to the best of our knowledge, this survey is the first to determine the factors associated with MMR infection and the need for MMR revaccination in PLWH in Iran.

Conclusion

MMR has been a great threat to immunosuppressed individuals, including PLWH, especially HIV-positive women of childbearing age, due to its complications. This research evaluated the need for MMR vaccine boosters in this group and revealed that WLWH were more susceptible to at least one of MMR viruses. We also illustrated that a lower CD4 NADIR may be a risk factor for developing mumps in the study population. These findings could imply that in cases of lower CD4 NADIR and if revaccination is not considered to be an emergency, patients could receive proper ART and that revaccination could occur after CD4 NADIR counts are greater than 200 cell/mm^3.

Abbreviations

HIV	Human Immunodeficiency Virus
MMR	Measles, Mumps and Rubella
ART	Anti-Retroviral Therapy
CD4	Cluster of Differentiation 4
PLWH	People Living with HIV
WLWH	Women Living with HIV
HPV	Human Papilloma Virus
VCT	Voluntary Counseling and Testing
ELISA	Enzyme-Linked Immunosorbent Assay
HIS	Hospital Information System
SD	Standard Deviation
IQR	Interquartile Range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12981-025-00735-7.

Supplementary Material 1

Acknowledgements

The authors thank the staff of the hospital for their help.

Author contributions

ER contributed to conceptualization, interpretation, project administration, data gathering, data validation and analysis, interpretation, reviewing, editing, and supervision. SG and KF contributed to writing the original draft, data validation, data analysis, interpretation, reviewing and editing. MH, SG, LA, SD, AA, and SA contributed to reviewing and editing. ER, as the corresponding author, had full access to all parts of the study and had the responsibility of submitting the manuscript for publication.

Funding

This research didn't receive grants from any funding agency in the public, commercial or not-for-profit sectors.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran. All methods were carried out in accordance with relevant guidelines and regulations. This study was conducted in an academic teaching/research hospital (Imam Khomeini Hospital Complex affiliated to Tehran University of Medical Sciences). In this academic center, all patients or their legal guardians are initially explained that their information and possible samples will be anonymously collected, reviewed, and reported in educational and research projects. The patients who give written consent to this issue will be included in the mentioned studies (like our study). Patients are allowed to freely choose whether or not their data be used in an anonymized database. Informed consent was obtained from all the patients and/or their legal guardian(s) for this study. This study was approved with ethics code: IR.TUMS.IKHC.REC.1402.128.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 11 October 2024 / Accepted: 22 March 2025
Published online: 03 April 2025

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