MAINTENANCE OF TETANUS, DIPHTHERIA AND PERTUSSIS ANTIBODIES AFTER PRIMARY IMMUNIZATION IN CHILDHOOD AND HUMORAL IMMUNE RESPONSE TO A Tdap BOOSTER IN VERTICALLY HIV-INFECTED ADOLESCENTS

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Introduction

Although the incidence of diseases such as tetanus, diphtheria and pertussis has declined after routine vaccination, outbreaks still occur worldwide, even in places with high vaccination coverage.

Many vertically HIV-infected children are now able to reach adolescence. However, they still develop a lower humoral immune response after vaccination and a faster decay of antibodies is observed despite the successful use of combined antiretroviral therapy (cART). After revaccination or following booster doses, the majority of HIV-infected youngsters reach protective antibody levels.

No study has assessed the immune response of vertically HIV-infected adolescents to Tdap so far. This study evaluated the humoral response after a Tdap booster dose in HIV-infected and in healthy adolescents.

Methods

Thirty HIV adolescents with CD4>200 on combined antiretroviral therapy (cART) and 30 healthy CONTROLS were immunized with Tdap. Subjects from both groups needed to meet the following criteria: aged between 10 and 24 years; to have had 3 doses of diphtheria-tetanus-whole-cell pertussis vaccine (DTwP) and at least one DTwP or tetanus-diphtheria (Td) booster dose with a minimum of a 3 year-interval from study entry. Pregnancy was an exclusion criterion for both groups, as well as moderate or severe acute infection diagnosed in the previous 15 days.

Individuals from HIV group had to be infected by vertical transmission and to have CD4+ T cells above 200 cells/mm³ on the last assessment. Individuals from CONTROL group should not present any chronic, autoimmune, allergic or neoplastic disease, or use of immunosuppressive medication.

Blood samples were collected immediately before and 28 days after Tdap.

Tetanus and diphtheria antibodies were tested with an in-house double antigen enzyme-linked immunosorbent assay. The reference sera used were obtained from the NIBSC, UK. Tetanus and diphtheria antibody levels greater than or equal to 0.1 IU/mL were considered protective. Pertussis toxin antibodies were tested using SERION ELISA classic *Bordetella pertussis*-IgG kit (Virion\Serion, Würzburg, Germany). As there is no pertussis correlate of protection, the cut-off of 62.5 IU/ mL was considered as suggestive of *B. pertussis* infection in the previous 12 months (80% sensitivity and 95% specificity). Individuals with pertussis toxin antibodies above 62.5 IU/mL on day 0 were excluded from seroconversion analysis. For individuals who had pertussis toxin antibody levels on day 0 below 62.5 IU/mL, seroconversion was considered when they were above 5 IU/mL starting from below this level; if baseline values were higher than 5 IU/mL, seroconversion was considered if values were at least twice the initial levels.

This study was approved by the Ethics Committee of the Universidade Federal de São Paulo and all parents/guardians signed the informed consent prior to enrollment (protocol number 777.149).

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Results

Table 1: Clinical and demographic characteristics of individuals from HIV and CONTROL groups at study entry

Parameters	HIV (n=30)	CONTROL (n=30)	p value
Female gender	15 (50.0%)	19 (63.3%)	.435
Average age in years (range)	17.9 (12.6-20.8)	17.1(11.8-23.5)	.227
Median body mass index (Q1-Q3)	20.0 (18.0-22.8)	22.0 (19.3-24.8)	.064
Individuals with undetectable HIV viral load or with <40 copies/mL	17/29 (58.6%)	n/a	-
Median undetectable viral load time in years (Q1-Q3)	4.6 (2.1-6.9)	n/a	-
Therapeutic regimen in use			
2 NRTI + 1 PI	25/30 (83.3%)	n/a	-
1 NRTI + 1 NNRTI + 1 PI	3/30 (10%)	n/a	-
2 NRTI + 1 NNRTI	2/30 (6.7%)	n/a	-
Meningococcal C tetanus toxoid vaccine between 2001 and 2015	21/30 (70%)	1/30 (3.3%)	<.001
CD4+ T cells/mm ³ at study entry	625.0 (331.4 - 868.3)	1012.1 (706.6 -1167.7)	<.001
CD8+ T cells/mm ³ at study entry	838.7 (583.3 - 1227.9)	631.1 (487.7 - 827.7)	.025

Table 2: Median antibody levels for tetanus, diphtheria and pertussis in the HIV and CONTROL groups on days 0 and 28. Individuals from the HIV and CONTROL groups with antibodies to tetanus and diphtheria below those considered protective and who did not present pertussis seroconversion on days 28 are also shown.

Parameter (IU/mL)	Day	Median antibody levels (Q1-Q3)		Mann-Whitney (p)	Individuals with antibodies below protective levels/ without seroconversion		Fisher's exact test (p)
		HIV	CONTROL		HIV	CONTROL	
Tetanus	0	0.4 (0.1-1.2)	0.1 (0.0-0.3)	.018	7 (23.3%)	11 (37.7%)	.398
	28	26.7 (13.7-42.4)	29.3 (8.8-46.6)	.626	1 (3.3%)	0 (0.0%)	>.999
Diphtheria	0	0.2 (0.0-0.6)	0.7 (0.1-1.3)	.165	11 (36.7%)	9 (30.0%)	.784
	28	4.0 (1.0-15.5)	22.9 (11.6-42.1)	<.001	3 (10.0%)	0 (0.0%)	.237
Pertussis	0	8.7 (2.7-37.0)	7.1 (4.7-17.1)	.489	-	-	-
	28	44.0 (11.8-79.5)	48.1 (23.9-140.1)	.152	11 (37.9%)	0 (0.0%)	.002

Conclusions

- Vertically HIV-infected adolescents on cART respond to a Tdap booster with lower humoral immune response, especially to diphtheria and pertussis antigens.
- Meningococcal tetanus toxoid conjugate vaccines might influence maintenance of tetanus antibodies after primary vaccine scheme.