Serum IgA inhibits HIV-specific broadly neutralising antibody Fc functions

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Background:
Macaque passive transfer studies of HIV-broadly neutralizing antibodies (BnAbs) suggest a vital role of Fc functions in protection. The importance of antibody Fc functions were highlighted in the human HIV RV144 vaccine trial, however, serum IgA reduced vaccine efficacy and protective Fc functions. Serum IgA can influence Fc effector cell functions, such as phagocytosis, via FcαR. When in complex with antigen, serum IgA can induce Fc functions, however, free IgA can inhibit Fc functions. Elucidating how serum IgA modulates Fc responses is essential. Here we endeavour to determine if serum IgA influences the Fc capacity of IgG from people living with HIV or BnAbs.

Methods:
Pooled purified IgG from HIV individuals (HIVIG) along with a panel of BnAbs including PGT121 and VRC01, currently in human clinical trials, were assessed for their Fc functional capacity. The influence of IgA upon IgG was assessed by adding pooled HIV-specific IgA (n=10), pooled HIV-negative IgA (n=10), IgA1 and IgA2.

Results:
HIV-specific IgA showed minor inhibition of phagocytosis (median=10.38%, IQR=8.09%, $p>0.05$). Intriguingly, significant inhibition was observed when HIV-negative IgA was added (median=21.24%, IQR=14.28%, $p<0.001$). Similarly, significant inhibition was observed with IgA1 (median=23.11%, IQR=18.18%, $p<0.001$) and IgA2 (median=19.88%, IQR=4.60%, $p<0.001$) when added to HIVIG and BnAbs. Addition of FcαR block to these assays was capable of reconstituting Fc functions, suggesting that IgA inhibition is mediated through IgA-FcαR binding.

Conclusion:
HIV-negative serum IgA, and to a lesser extent HIV-positive IgA, reduced the functional capacity of HIVIG and BnAbs, suggesting IgA may inhibit through IgA-FcαR mediated inhibitory mechanisms. Understanding the mechanisms behind why IgA inhibits Fc responses could lead to improved future HIV vaccine design and educate passive transfer monoclonal antibody therapies. Elucidating the extent of IgA inhibition of Fc functions of different BnAbs will help inform tailor-made passive transfer treatments for HIV prevention, control and cure.

Disclosure of Interest Statement:
The Australasian Society for HIV, Viral Hepatitis & Sexual Health Medicine recognises the considerable contribution that industry partners make to professional and research activities. We also recognise the need for transparency of disclosure of

potential conflicts of interest by acknowledging these relationships in publications and presentations.

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