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Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: A partially-blind randomised placebo-controlled study☆

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ABSTRACT

In developing countries, risk of human papillomavirus (HPV) infection may be increased by the high prevalence of human immunodeficiency virus (HIV) infection. We evaluated the safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-infected women in South Africa. Asymptomatic HIV-positive women aged 18–25 years ($N = 120$) were stratified by $CD4^+$ T-cell count and randomised (1:1) to receive HPV-16/18 vaccine (*Cervarix*®; GlaxoSmithKline Vaccines) or placebo ($Al[OH]_3$) at 0, 1 and 6 months (double-blind). HIV-negative women ($N = 30$) received HPV-16/18 vaccine (open label). Anti-HPV-16/18 antibody and $CD4^+$ T-cell responses, $CD4^+$ T-cell count, HIV viral load, HIV clinical stage and safety were evaluated for 12 months. The safety and reactogenicity profile of the HPV-16/18 vaccine was comparable in HIV-positive and HIV-negative women. Irrespective of baseline HPV status, all HIV-positive and HIV-negative women who received the HPV-16/18 vaccine were seropositive for both HPV-16 and HPV-18 after the second vaccine dose (month 2) and remained seropositive for both antigens at month 12. Anti-HPV-16/18 antibody titres at month 12 remained substantially above levels associated with natural infection. The HPV-16/18 vaccine induced sustained anti-HPV-16/18 $CD4^+$ T-cell responses in both HIV-positive and HIV-negative women. No impact of baseline $CD4^+$ T-cell count or HIV viral load was observed on the magnitude of the immune response in HIV-positive women. In HIV-positive women, $CD4^+$ T-cell count, HIV viral load and HIV clinical stage were unaffected by HPV-16/18 vaccine administration. In conclusion, the HPV-16/18 AS04-adjuvanted vaccine appears immunogenic and well-tolerated in women with HIV infection.

Study ID: 107863/NCT00586339.

1. Introduction

Over 85% of cervical cancer cases and related deaths occur in developing countries [1], with approximately 80,000 women diagnosed with cervical cancer and around 60,000 women dying from this disease annually in Africa [2]. Persistent infection of the cervix with high-risk human papillomavirus (HPV) types is necessary for the development of invasive cervical cancer [3]. Among the HPV types currently considered oncogenic, HPV-16 and HPV-18 are the most common cumulatively accounting for over 70% of cervical cancer cases worldwide [4].

There appears to be an association between human immunodeficiency virus (HIV) and HPV infection [5–10], with the cervical cancer and HIV infection epidemics having a strong geographic correlation in sub-Saharan Africa. There are an estimated 22.5 million people living with HIV in sub-Saharan Africa, representing 68% of

Abbreviations: APC, antigen-presenting cell; ART, antiretroviral therapy; ATP, according-to-protocol; BARC, Bio Analytical Research Corporation; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean antibody titre; HPV, human papillomavirus; HIV, human immunodeficiency virus; IDMC, Independent Data Monitoring Committee; MPL, monophosphoryl lipid A; NOCD, new-onset chronic disease; PMTCT, Preventing Mother-to-Child Transmission of HIV; SAE, serious adverse event; TVC, total vaccinated cohort; WHO, World Health Organisation.

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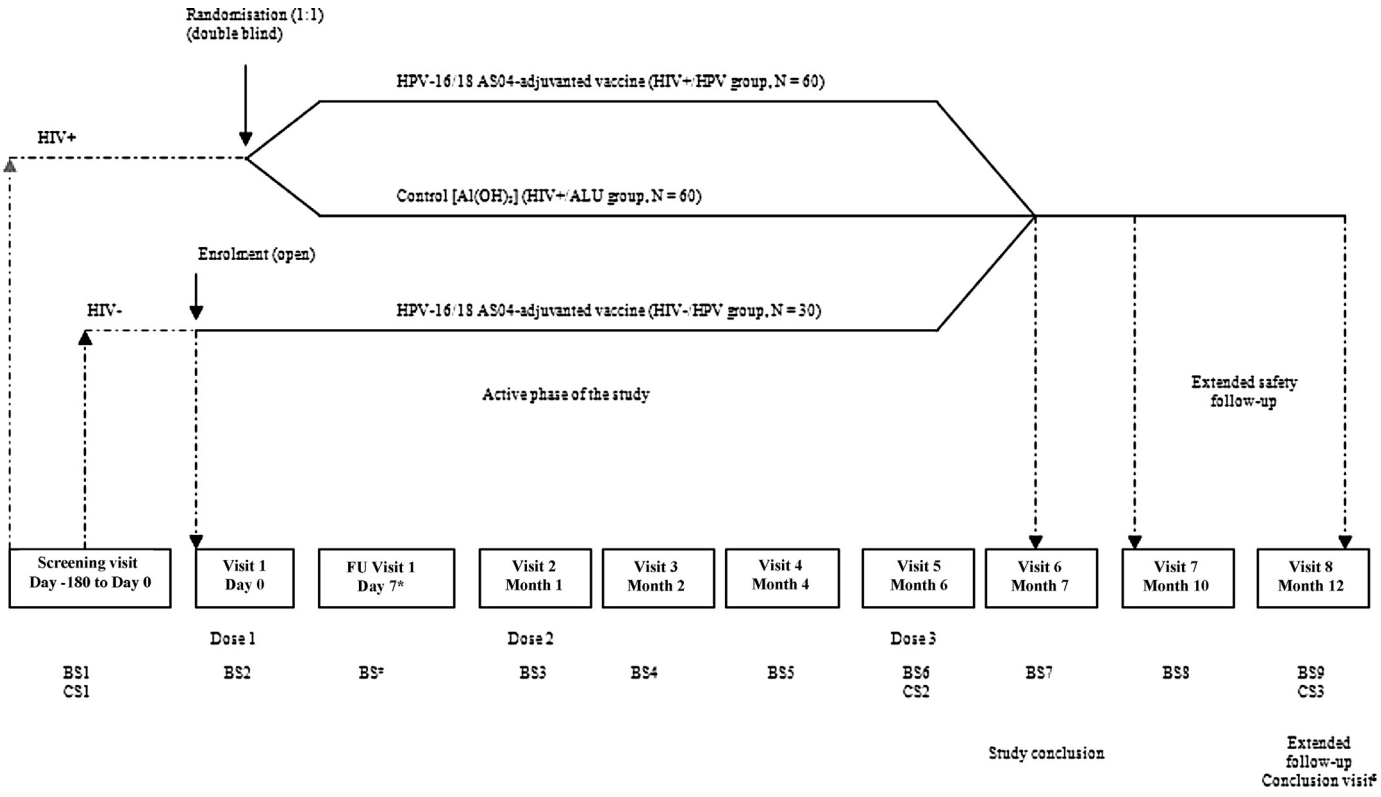

BS: Blood sample; CS: Cervical sample.
* Pregnancies and their outcome will be followed until delivery (even if delivery occurs after the end of the extended safety follow-up period [Month 7 – Month 12])
# 30 HIV+ subjects with CD4+ count >200/mm3 and HIV- subjects (enrolment Part A) will have an extra visit at Day 7 (Follow-up [FU] Visit 1) to return their diary cards and have a blood sample collected for evaluation of biochemical and haematological parameters.

Fig. 1. Study design.

the global HIV burden [11]. The majority of people living with HIV in sub-Saharan Africa are female, mainly girls and women aged 15–24 years, with approximately 21% of women aged 20–24 years known to be infected with HIV. In a case–control study in South Africa, HIV-positive women were 5 times more likely to be infected with high-risk HPV types than HIV seronegative women [12].

The HPV-16/18 AS04-adjuvanted vaccine is well-tolerated, immunogenic and highly effective against persistent HPV infection and associated cervical lesions in HIV-negative young women [13–19]. This study assessed the safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in young women with HIV infection from South Africa. Once HPV vaccination is implemented in the public health sector in African countries, it is unlikely that the HIV status of vaccine recipients will be known and girls and women with undiagnosed HIV infection will likely be vaccinated against HPV. It is therefore imperative that there is a clear understanding of the safety and immunogenicity of the HPV-16/18 vaccine in HIV-positive women.

2. Methods

2.1. Study participants

This was a Phase I/II, partially-blind, partially-randomised, placebo-controlled trial at a single centre in Khayelitsha, Cape Town, Republic of South Africa. Women aged 18–25 years at the time of first vaccination with an intact cervix who reported no more than six lifetime sexual partners and who the investigator believed would comply with the protocol requirements were eligible for inclusion. Pregnant women were excluded. Sexually active women had to have a normal colposcopy and a normal cervical cytology or no greater than atypical squamous cells of undetermined significance at the screening visit. All women had to be willing to undergo HIV counselling and testing and to be informed of their HIV status.

HIV-positive women had to be in World Health Organisation (WHO) Clinical Stage 1 [20]. Women on antiretroviral therapy (ART) had to be compliant with treatment and have a HIV viral load $\leq$400 copies/mm^3 for at least 6 months. Women confirmed as HIV seronegative were eligible to participate in the HIV-negative control group. HIV-positive women were followed during the study in accordance with WHO guidelines [21]. Women eligible for ART were referred to the Primary Health Care HIV Clinic which provided access to medical care according to local guidelines [22]. HIV-positive women found to be pregnant were referred to the Preventing Mother-to-Child Transmission of HIV (PMTCT) programme. HIV-negative women who seroconverted were referred for counselling and follow-up.

Informed consent was obtained from all women and approval was obtained from the Human Research Ethics Committee of the University of Cape Town and the Medicines Control Council of South Africa prior to study start.

2.2. Study design

Study design is summarised in Fig. 1. HIV-positive women were randomised (1:1) to receive the HPV-16/18 AS04-adjuvanted vaccine (*Cervarix*®*, GlaxoSmithKline Vaccines) (HIV+/HPV group) or $Al(OH)_3$ control (HIV+/ALU group) at 0, 1, and 6 months in a