Contraceptive use among women attending an open access genitourinary medicine department. Trewinnard K, Foley E. *Int J STD AIDS* 2009; **20**: 573–574

In this short audit report, Trewinnard and Foley looked at contraception use in women attending a walk-in genitourinary medicine (GUM) clinic at the South Hants Hospital in Southampton, UK.

It is known that abortion rates in the UK are rising, especially in the under-20s, and that this is occurring despite an increase in the use of condoms. Women presenting repeatedly for termination of pregnancy usually rely on condoms and have a poor uptake of long-acting reversible contraceptives (LARCs). Many women attending GUM clinics for sexually transmitted infection (STI) screening do so because of unprotected sexual intercourse and therefore are at risk of pregnancy if condoms are their only method of contraception. The audit was carried out as part of a service evaluation assessing provision for the wider sexual health needs for those attending GUM clinics.

The audit was carried out prospectively with a questionnaire offered to the female attenders of reproductive age who were sexually active between March and April 2008. A total of 152 women with a mean age of 26 years completed the questionnaire, which appears to be a low response rate as it represented 17% of the women seen during the study. 87.5% reported use of at least one contraceptive method. 64% of women reported using a reliable method of contraception and of these 76% used pills, 14% used a LARC and 3% had been sterilised. 28% were using condoms (which were considered unreliable) and 36% were not using any reliable method.

Overall 38% of respondents asked for further contraceptive advice. Of those using an unreliable method, 50% asked for advice; whereas of those using a reliable method, only 28% asked for further advice. Some 15% of women were obtaining contraception from a family planning clinic, 55% obtained contraception from a general practitioner, and the remainder bought condoms or obtained them from GUM clinics.

In their discussion the authors reported use of contraception being comparable to women generally in the UK, and that they had a higher percentage (i.e. 28% vs 18%) of women relying on condoms alone compared to the UK population. They put this down to over-reporting due to patients' perception of health care professionals in the GUM setting. They also noted that many women were willing to ask for further advice and would accept the contraception provision in the GUM setting, and concluded that it would be cost effective to provide a full range of contraception in the GUM setting.

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Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, *et al*.; for the MOPH-TAVEG Investigators. *N Engl J Med* (www.nejm.org), 20 October 2009; 10.1056/NEJMoa0908492

This paper reports a multi-centre, placebo-controlled, randomised, double-blind trial, undertaken in Thailand with a community-based sample of over 16 402 men and women aged 18–31 years. Analysis of study data found that a combined ALVAC-HIV and AIDSVAX B/E vaccine regimen provided some protective effect against HIV infection. However, among individuals who contracted HIV infection, there was no difference in effect (active vs placebo) on viral load or CD4+ count, in the period up to 6 weeks after the detection of HIV infection.

The regimen was administered in four doses: at entry (Day 0), and at 4, 12 and 24 weeks later. Attempts were made to recruit all individuals in the community and, while there were some clinical exclusion criteria (e.g. tuberculosis), there was no selection by HIV risk. Pregnant or breastfeeding women were excluded, and women recruited were advised to practise effective contraception until 3 months after their last vaccine dose. Potential recruits were given a screening blood test to exclude individuals already infected with HIV. Participants were followed up at 24 and 26 weeks, and every 6 months thereafter, until the end of 42 months. For all women there was urine specimen testing for pregnancy at each dose of the vaccine regimen, and any pregnancy found meant no further vaccination. HIV testing was undertaken at Day 0 (which might have been some time after screening HIV test) and at all follow-ups.

Vaccine efficacy % (VE) was defined as 100 × (1 – hazard ratio for HIV infection, for vaccine group relative to placebo). [Thus, if in a proportional hazard time-to-HIV-infection analysis, the hazard ratio for vaccine relative to placebo was 0.45, then VE = 55%.] VE can be interpreted as the reduction in the rate of infection (across time) in the vaccinated group, relative to the placebo group. Sample size needed so as not to miss a VE of 50% was calculated at 16 000, on an expected rate of infection of 0.34%/year, if unvaccinated.

Of 26 676 individuals assessed for eligibility, 418 were screened as already infected with HIV, 8780 withdrew from further involvement, 976 were excluded (mainly for clinical reasons) and the remaining 16 402 underwent randomisation, to placebo or active vaccine, and commenced the regimen. However, a total of 3853 (23%) participants did not complete the trial as per protocol, these being in the vast majority of cases mistimed doses or receipt of fewer than four doses. In addition, it was subsequently established that seven individuals (five active arm and two placebo) had started treatment already infected with HIV – the presumption being that seroconversion occurred between screening test and Day 0. The total of 52 985 person-years of follow up obtained was more than had been calculated as needed.

Three main analyses of vaccine efficacy were undertaken: the standard intention-to-treat (ITT) analysis (*n* = 16 402, including all those randomised, regardless of adherence to protocol), a 'modified ITT' (*n* = 16 395, excluding only the seven inadvertently randomised/included but who, on later testing of Day 0 blood sample, were found to have been be HIV positive by the time of first dose) and 'per protocol' (*n* = 12 542, after excluding the 3853 individuals for whom there were deviations from protocol).

The two randomised groups were similar with respect to baseline characteristics, and 47% were classified as 'low risk' for HIV infection. In total, 132 HIV infections were detected (0.8% of individuals). The standard ITT and 'per protocol' analyses reported very similar vaccine efficacy: 26.4% and 26.2%. If the VE is indeed similar regardless of whether vaccine was administered per protocol or not, then this is promising for any future consideration of a population intervention. However, the small number of events (infections) involved meant that the estimates had wide confidence intervals (CIs), and there was inadequate power to reject the null hypothesis (VE = 0). The substantially smaller *n* for the per protocol analysis (down by 23%) and, crucially, the smaller number of infections remaining (86 instead of 132), meant that the precision of estimation of VE 'per protocol' was poorer (wider CI), and the power of testing the null hypothesis was lower (so that the p values for the two analyses of essentially identical 'effect' – VE of 26% – were a borderline 0.08, and a non-significant 0.16).

The third analysis, 'modified ITT', excluded only the seven individuals who had become HIV positive between screening (as eligible for the study) and first dose of treatment – those for whom there was no possibility of preventing HIV infection, because it predated all vaccine doses. This exclusion/modification is well described and eminently reasonable. Infection rates overall were 0.28%/year in the placebo group and 0.19%/year in vaccine group, and the VE estimate (31.2%) was marginally better than that for full ITT analysis. This is because by chance the excluded 'no hope' participants had been unluckily weighted against the vaccine arm – 5 to 2. Despite the marginally smaller number of infections for the modified ITT analysis (by 7), the higher VE found meant a p value of 0.04 for the hypothesis test of no effect, just significant at the conventional 5% threshold. However, while this VE might be statistically different from zero, it is almost as imprecisely estimated as for the full analysis, with true population VE having 95% CI of 1% to 51%. The paper also reported VE estimates by subgroups based on key characteristics (e.g. age, risk group), but clearly these subgroup estimates would be even less reliably estimated than the overall VE!

The discussion of the paper focuses on mechanisms for vaccine effect and immune response, presumably on account of the apparent contradiction within the results (under current immunological theory) between the VE effect found, and the fact that among those testing positive for HIV infection, there was no difference between vaccine and placebo participants in viral load in the 6 weeks after infection. While there is mention of 'lack of power', there is no reflection as to why the study turned out to be underpowered. Part of the explanation would appear to be a lower than expected infection rate in the placebo group (0.28% vs 0.34% used in sample size calculation), but the main reason is the low VE found – 31% (or 26%), rather than the 50% used in the sample size calculation. This lack of power exacerbates a fundamental uncertainty that pertains in all trial reports, namely that we do not know for sure that the true population effect is at least as good as the point estimate from the sample (VE = 31%). The CIs reported remind us that the true effect might also be lower than the point estimate, and in this study, 'lower' might mean considerably lower.

Nor is there reflection on the public health potential of a vaccine with an efficacy of around 30%. If a minimum of 50% VE was used for sample size calculation then one implication is that anything lower, in particular 31%, is deemed clinically unimportant. However, the likelihood is that the 50% minimum threshold for VE was used to ensure the study was feasible at all (i.e. did not require excessive sample size and/or time to results). It would have been helpful to have discussion of this and, given the uncertainty in the estimate, reflection on what might be a minimally useful effect for public health.

A pragmatic view must be that in the absence of any better vaccine being available, the ability to protect against infection as many as 31% of the entire world's communities at risk would be a profound global public health boon. If that is so, then a public health debate will be needed as to whether this would be a feasible and affordable goal, taking into account: the regimen required (four doses across 24 weeks); potential side effects (e.g. if taken by pregnant women, or if awareness of having been vaccinated adversely affected risk behaviour); whether screening of all individuals for HIV would be required prior to vaccination; and cost.

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