

# Interpretation of Serum $\alpha$ -fetoprotein, Human Chorionic Gonadotrophin and the Risk of Down's Syndrome in Pregnant Women Infected with HIV

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## Background

In the UK 90% of HIV positive (HIV+) women are of reproductive age and increasing numbers are having children. Maternal serum genetic screening is routinely offered; often comprising a triple assay of serum  $\alpha$ -fetoprotein ( $\alpha$ FP), human chorionic gonadotrophin (hCG) and unconjugated estriol (uE3). Previous studies have shown variation in hCG and  $\alpha$ FP levels with HIV status and treatment regimen. Raised levels of hCG are associated with an increased risk of Down's syndrome and the screen-positive rate may be higher in HIV+ compared with HIV negative (HIV-) women. We have sought to confirm and extend these findings.

## Methods

Triple assay results of all HIV+ pregnant women attending antenatal clinics at participating centres (2003-6) were reviewed and matched with HIV- women. Continuous variables were compared for using paired or unpaired t-tests as appropriate. Data from the National Study of HIV in Pregnancy and Childhood (NSHPC), the national surveillance scheme for obstetric and paediatric HIV in the UK and Ireland, were used to determine the incidence of Down's syndrome in live births and terminations.

## Results

Ninety-four HIV+ women met the study criteria. Forty-eight were antiretroviral untreated (ART-); 46 were antiretroviral treated (ART+). Of these 24 were PI un-exposed (ART+PI-); 22 were PI exposed (ART+PI+).

## Matched Studies

Seventy-seven women were successfully matched with HIV- women to within preset parameters. No adequate match was found for 17 women. Four women were screen-positive (risk >1:250) in the HIV+ group compared with three in the HIV- group. No difference in  $\alpha$ FP and uE3 levels related to HIV status alone was observed.

**hCG MOM (multiples of the median) was significantly higher in the HIV+ group compared with the HIV- group;** 1.33 versus 1.08 ( $p=0.028$ ; Graph 1).

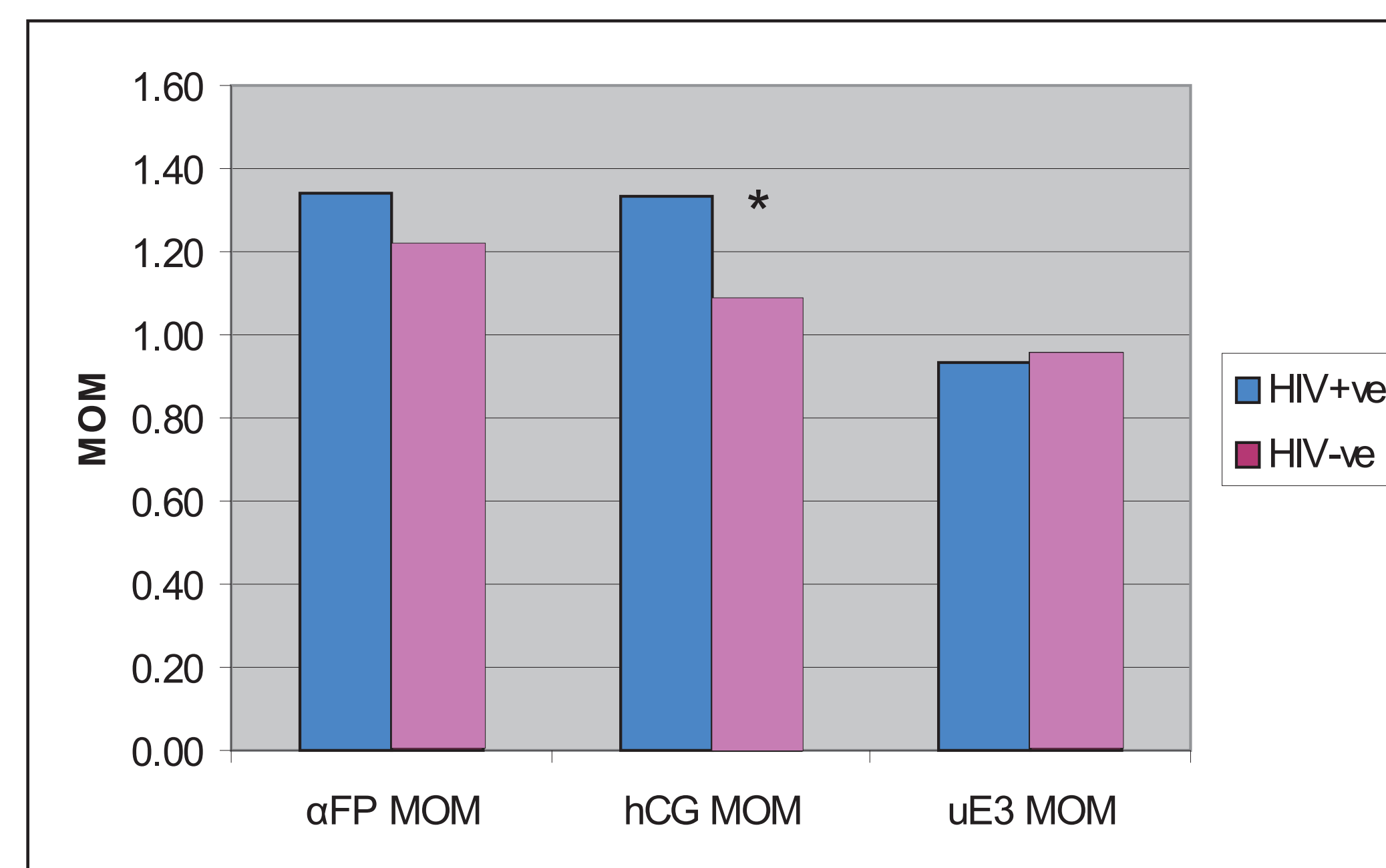
**$\alpha$ FP was significantly lower in the treated HIV+ group compared with HIV- controls;** 1.33 versus 1.07 ( $p=0.02$ ).  $\alpha$ FP appears to be modified by treatment rather than HIV status *per se*. There was no difference in uE3 levels by HIV status.

**Table 1:** Pre-screening (age-related) risk and post-screening (Down's) risk of Down's syndrome in HIV+ women and matched controls. The women were further subdivided into ART+ and ART- groups with their HIV-, ART unexposed matched controls.

All figures are quoted as a ratio of risk (1:x).

		ALL	ART+	ART-
HIV+	Age Risk	486	381	699
	Down's Risk	657	1091	452
HIV-	Age Risk	486	390	629
	Down's Risk	783	1233	1085
<i>p</i> -value		0.72	0.34	0.22

**Graph 1:** The effect of HIV status on alpha-fetoprotein, human chorionic gonadotrophin and unconjugated estriol 3 levels in pregnant women

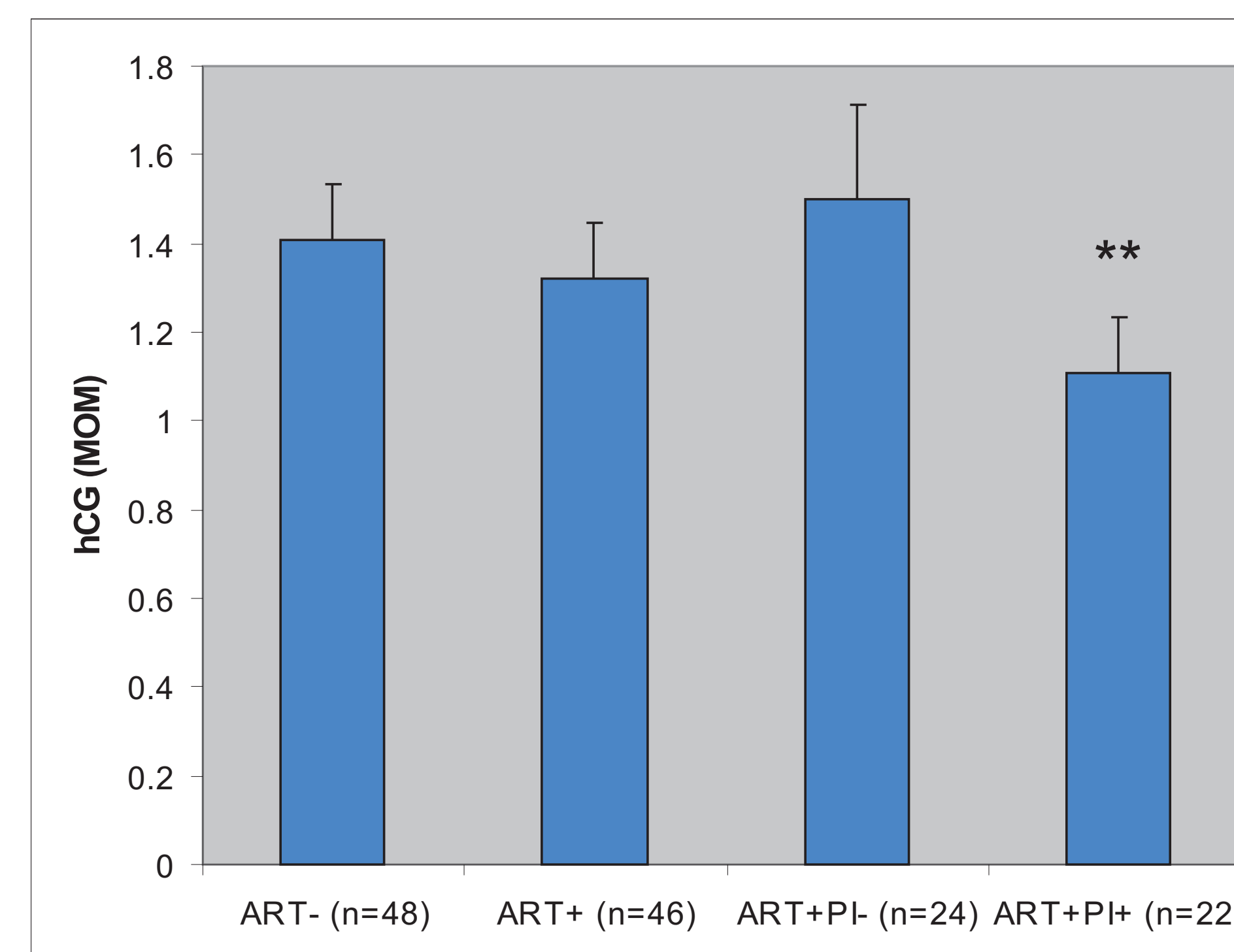


\* HIV-ve vs HIV+ve  $p=0.028$

## Non-matched Studies

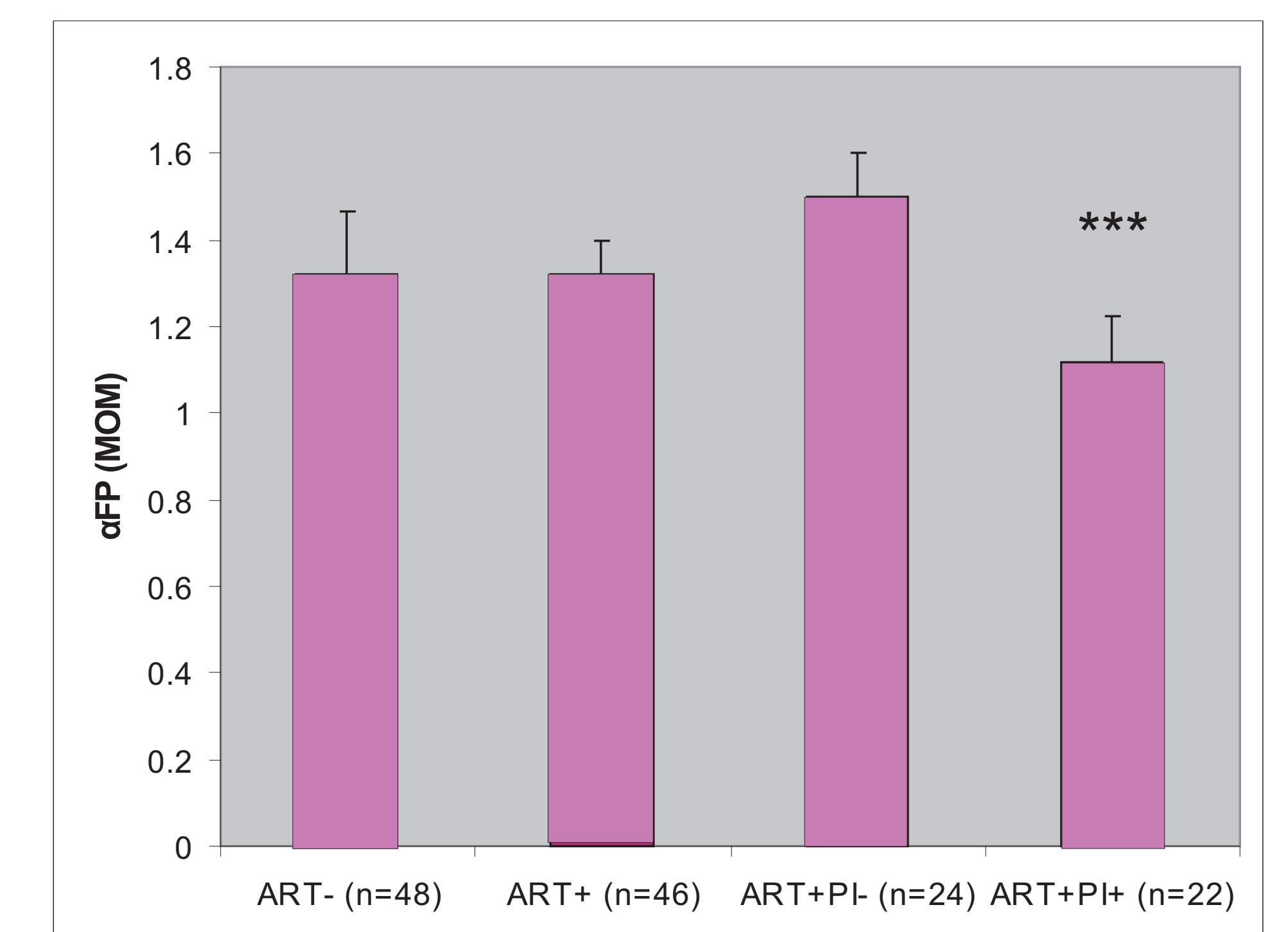
All ninety-two women were included in the regimen-comparison studies. **Treatment regimens containing PIs were associated with significantly reduced  $\alpha$ FP MOM compared with other treatment regimens** ( $p=0.01$ ) (Graph 3). There was a non-significant trend for the ART+PI+ group to have lower hCG MOM than the untreated ( $p=0.14$ ) and ART+PI- ( $p=0.12$ ) groups (Graph 2). There was no difference in uE3 levels by treatment regimen.

**Graph 2:** The effect of treatment regimen on hCG MOM



\*\* ART+PI- vs ART+PI+  $p=0.12$

**Graph 3:** The effect of treatment regimen on  $\alpha$ FP MOM



\*\*\* ART+PI- vs ART+PI+  $p=0.012$

## Screen adjusted risk of Down's syndrome (Table 1)

In the matched study, the age-related risk was 1/486 for both groups, confirming good matching. There was a non-significant ( $p=0.723$ ) **increase in post-screening calculated Down's risk in the HIV+ group compared with the HIV- group** (1/657 compared to 1/782). Untreated HIV+ women appear to have greater post-screening risk than those receiving ART.

## Epidemiological data

5763 pregnancies in HIV+ women were recorded by the NSPHC database from 1994 to 2006. The expected incidence of Down's syndrome in this population is 10 (95% confidence interval = (7.65, 23)) based on population age composition. The observed incidence of Down's Syndrome was 14 (1/412 pregnancies), and does not differ significantly from the expected one.

## Conclusion

Human chorionic gonadotrophin is raised in HIV+ women, although hCG concentrations appear to be normalised by PI+ regimens.

PI-based therapy, but not HIV *per se*, tended to be associated with decreased  $\alpha$ FP levels.

These biochemical changes will tend to increase the predicted screen-adjusted risk of Down's syndrome in HIV+ women, particularly those not on a treatment regimen containing a protease inhibitor.

Epidemiological data does not support the hypothesis that there is an observed increase in Down's syndrome in the children of HIV+ women. Therefore the increase in predicted risk may be associated with false-positive screening results.

We would suggest that serum-screening for Down's syndrome in the HIV+ population should be treated with caution and perhaps more robust methodologies should be used to avoid unnecessary parental concern, amniocentesis and terminations.



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