	Pre-terlipressin (n=8)	2 h post-terlipressin (n=8)	6 h post-terlipressin (n=8)	12 h post-terlipressin (n=8)	24 h post-terlipressin (n=6)	Overall p
Mean arterial pressure (mm Hg)	52 (3)	72 (7)*	65 (5)*	62 (7)†	69 (5)	0·005
Norepinephrine (μg/kg per min)	0·59 (0·22)	0·29 (0·18)†	0·25 (0·16)†	0·28 (0·25)†	0·19 (0·26)	0·002
survivors (n=4)	0·68 (0·19)	0·26 (0·26)	0·17 (0·14)	0·14 (0·10)	0·08 (0·03)	··
non-survivors (n=4)	0·50 (0·24)	0·31 (0·09)	0·34 (0·14)	0·42 (0·29)	0·71, 0·17 (n=2)	··
Cardiac output (L/min)	8·1 (1·6)	6·4 (2·0)†	6·6 (1·9)‡	7·0 (1·0)	7·1 (1·5)	0·014
Heart rate (beats per minute)	109 (12)	103 (15)	99 (18)‡	99 (15)‡	94 (10)	0·049

Data are mean (SE). One-way repeated measures ANOVA with post-hoc Bonferroni *t* tests done up to 12 h post-terlipressin (not to 24 h because of two informative missing datapoints): *p<0·001, †p<0·01, ‡p<0·05 *vs* baseline values.

Table 2: **Haemodynamic variables and norepinephrine dose**

Low-dose vasopressin (0·01–0·04 IU per min) is an effective pressor agent in about 85% of patients with norepinephrine-resistant hypotension.[1–3] However, discontinuation of vasopressin results in rapid hypotension, requiring immediate resumption of vasopressin, or increase in norepinephrine. Tsuneyoshi and colleagues[3] reported an average duration of vasopressin infusion of 93 h (range 18–284) in 14 patients with septicaemia who had a significant pressor response. We cannot explain why a single bolus of terlipressin was an effective treatment in our patients, despite their much higher baseline norepinephrine requirements (mean 0·59 [SD 0·08] *vs* 0·25 [0·01] μg/kg per min in the Tsuneyoshi study). Interaction with the previously administered steroids or methylene blue, or both, might be relevant but requires confirmation.

Vasopressin, an endogenous hormone produced in the hypothalamus, is released from the posterior pituitary gland in response to increased plasma osmolarity, hypovolaemia, and hypotension. Concentrations of vasopressin in plasma consistently rise in cardiogenic and hypovolaemic shock states but, for unknown reasons, are inappropriately low in sepsis. Landry and co-workers[1] reported mean plasma concentrations of 1·45 (0·15) pg/mL in healthy individuals and 22·7 (2·2) pg/mL in 12 patients with cardiogenic shock, but only 3·1 (1·0) pg/mL in 19 patients with septicaemia with similar blood pressures. An infusion of vasopressin (0·01 units per min) was sufficient to raise plasma concentrations to 30 pg/mL, with corresponding rises in systolic blood pressure (83–115 mm Hg) and a reduction in norepinephrine requirements.

V_1-receptor stimulation in vascular smooth muscle produces more potent vasoconstriction than either angiotensin II or norepinephrine. The lack of pressor response in non-septic patients might be related to an intact baroreflex response, resulting in heart rate reductions. The absence of a large negative chronotropic effect to terlipressin in our study concurs with previous findings.[1–3] Mechanisms underlying increased pressor sensitivity to vasopressin and its analogues in septic shock remain unknown. Using human gastroepiploic arteries, Hamu and colleagues[4] showed that vasopressin, acting on V_1 receptors, potentiated responses to norepinephrine in normal and endotoxin-treated tissues. Similarly, vasopressin potentiated the vasoconstrictor effects of norepinephrine, electrical field stimulation, and potassium chloride depolarisation, effects mediated via an increase in intracellular calcium through voltage-dependent calcium channels.[5]

Overall survival rates of 40–50% are quoted for septic shock, though anticipated mortality would be much higher in the subset who fail to respond to high-dose norepinephrine plus dexamethasone and methylene blue rescue therapy. Terlipressin offers a potentially important and inexpensive therapeutic alternative in hypotensive septic patients not responding to high-dose catecholamine therapy, which seems safe and is easy to administer. The response to a single dose suggests restoration of vascular reactivity, and thus enhanced sensitivity to endogenous and exogenous catecholamines. Our findings also provide a new perspective on the pathophysiology underlying sepsis-induced vascular hyporeactivity.

Contributors
A O'Brien and M Singer had the original idea for the study and did the clinical work. A O'Brien, L H Clapp, and M Singer jointly interpreted the data and wrote the report.

Conflict of interest statement
None declared.

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Vitamin A deficiency and genital viral burden in women infected with HIV-1

Audrey L French, Mardge H Cohen, Stephen J Gange, Harold Burger, Wei Gao, Richard D Semba, William A Meyer III, Esther Robison, Kathryn Anastos

The relation between vitamin A (retinol) deficiency and perinatal transmission of HIV-1, if it exists, might be mediated through an increased viral load in the mother's genital tract. To ascertain whether or not such an association is present, we measured the serum concentration of retinol with high performance liquid chromatography, and correlated the results with concurrent quantified HIV-1 RNA concentrations in cervicovaginal lavage fluid in 301 women infected with the virus. We noted no association between retinol status and genital HIV-1 load. Our findings lend support to those of studies that reported no association between retinol deficiency and perinatal HIV-1 transmission.

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An association between vitamin A (retinol) deficiency and perinatal transmission of HIV-1 has been reported in African

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	All (n=301)	Retinol <1·05 μmol/L (n=52)	Retinol ⩾1·05 μmol/L (n=249)	Odds ratio (95% CI)	p
Age (mean, SE) (years)	37·7 (0·4)	38·3 (0·9)	37·6 (0·5)	1·0 (1·0–1·1)	0·50
Ethnic origin	..	..	..	..	0·42
Black	156 of 300 (52%)	30 of 52 (58%)	126 of 248 (51%)	1·0	..
White	22 of 300 (7%)	2 of 52 (4%)	20 of 248 (8%)	0·4 (0·1–1·9)	..
Latin American or Hispanic	118 of 300 (39%)	19 of 52 (37%)	99 of 248 (40%)	0·8 (0·4–1·5)	..
Other	4 of 300 (1%)	1 of 52 (2%)	3 of 248 (1%)	..	..
Risk category	..	..	..	..	0·006
Injection drug user	112 of 298 (38%)	30 of 52 (58%)	82 of 246 (33%)	2·1 (0·9–5·3)	..
Heterosexual	133 of 298 (45%)	15 of 52 (29%)	118 of 246 (48%)	0·75 (0·3–2·0)	..
None identified	48 of 298 (16%)	7 of 52 (14%)	41 of 246 (17%)	1·0	..
Transfusion	5 of 298 (2%)	0	5 of 246 (2%)	..	..
CD4 count (mean, SE) (cells/mm³)	362 (15·6)	362 (35·4)	362 (17·4)	1·0 (0·9–1·1)	0·96
Detectable plasma HIV-1 RNA	261 of 274 (95%)	45 of 49 (92%)	216 of 225 (96%)	0·5 (0·1–1·6)	0·25
Plasma HIV-1 RNA (median, IQR)* (copies/mL)	26 683 (5281–90 813)	22 893 (3650–79 934)	29 321 (5549–102 967)	0·8 (0·6–1·1)	0·10
Detectable genital HIV-1 RNA	133 of 301 (44%)	25 of 52 (48%)	108 of 249 (43%)	1·2 (0·7–2·2)	0·54
Genital HIV-1 RNA (median, IQR)* (copies/mL)	3195 (523–12 476)	1968 (523–9806)	3238 (528–12 532)	0·9 (0. 8–1·1)	0·24
Treatment	..	..	..	..	0·34
None	205 of 299 (69%)	40 of 52 (77%)	165 of 247 (67%)	1·0	..
Single NRTI	87 of 299 (29%)	11 of 52 (21%)	76 of 247 (31%)	0·6 (0·3–1·2)	..
Dual NRTI	7 of 299 (2%)	1 of 52 (2%)	6 of 247 (2%)	0·7 (0·1–5·9)	..
HAART	0	0	0		..
Genital infection†	161 of 293 (55%)	30 of 511 (59%)	131 of 242 (54%)	1·2 (0·7–2·2)	0·54
Pregnant	2 of 294 (1%)	0	2 of 243 (1%)	..	0·68
Body-mass index (mean, SE) (kg/m²)	26·9 (0·4)	26·1 (0·9)	27·0 (0·4)	1·0 (0·9–1·0)	0·19
Serum albumin (mean, SE) (g/L)	41 (0·3)	39 (0·7)	42 (0·3)	2·0 (0·1–0·5)	<0·0001

Data are numbers (%) unless otherwise indicated. NRTI=nucleoside reverse transcriptase inhibitor; HAART=highly active antiretroviral therapy. *For detectable values; †gonorrhoea, chlamydia, trichomonas, or bacterial vaginosis present at time of visit.

Factors associated with low serum retinol concentrations in 301 women infected with HIV-1

and US studies, but reports have been inconsistent.[1–3] Retinol is essential for maintenance of genital mucosal integrity, since it regulates differentiation of ectocervical epithelial cells and expression of cytokeratins. An association between retinol deficiency and perinatal transmission, if it exists, could be partially mediated through an increased burden of HIV-1 in the female genital tract.[2] Although results of studies of African women[4,5] have indicated an association between retinol deficiency and detectable HIV-1 DNA in vaginal secretions, the relation between retinol and quantified HIV-1 RNA in female genital secretions remains unknown. Our aim was to explore this relation.

We used a subset of data obtained as part of the Women's Interagency HIV Study (WIHS), a longitudinal US trial of women with, or at risk of contracting, HIV-1, which began in 1994 before the general availability of potent antiretroviral therapy. At the baseline WIHS visit, all individuals provided written informed consent, and blood and genital specimens were obtained. Cervicovaginal lavage (CVL) was done with a 10 mL syringe filled with sterile, non-bacteriostatic saline aimed directly at the cervical os. The pooled fluid was aspirated from the vaginal vault and frozen within 28 h of collection. Serum and CVL fluid were stored at -70° C in a light-protected environment.

We measured and correlated serum concentrations of retinol with concurrent HIV-1 RNA measurements from CVL fluid, taken from the 301 of the 418 women infected with HIV-1 and enrolled in the WIHS study at the Bronx, NY, USA, site who had stored serum and CVL fluid available for testing. We measured serum retinol with high performance liquid chromatography, and judged values of less than 1·05 μmol/L as low and consistent with deficiency.[2] We quantified HIV-1 RNA in CVL fluid and plasma with a nucleic acid sequence based assay (NASBA, NucliSens, bioMerieux, Durham, NC, USA) with lower limits of detection of 80 and 40 copies/mL, respectively. We assigned undetectable values half the limit of detection for statistical analysis.

We assessed associations between categorical variables with the χ^2 test, and compared groups with respect to continuous variables with independent samples *t* test or non-parametric Mann-Whitney. We obtained correlations between $\log_{10}$ absolute retinol concentrations and $\log_{10}$ plasma HIV-1 RNA, and $\log_{10}$ CVL HIV-1 RNA by use of Spearman correlations. A sample size of 301 ensures a power of 93% for detection of a correlation of 0·2 or greater.

The table shows the demographic and disease characteristics of the 301 women studied. The figure shows that there was a significant correlation between plasma HIV-1 RNA and CVL HIV-1 RNA (correlation coefficient 0·33, p<0·0001), but no correlation between serum concentrations of retinol and CVL HIV-1 RNA (0·00, p=0·87). Women with detectable and undetectable CVL HIV-1 RNA had the same log of absolute retinol concentrations (p=0·81). The frequency of detectable CVL HIV-1 RNA (p=0·54) and absolute CVL HIV-1 RNA (p=0·24) did not differ between women who had low or normal retinol concentrations. The Spearman correlation coefficients were not significant when subgroups were analysed: injection drug users (−0·11, p=0·21) or women who acquired HIV-1 heterosexually (0·03, p=0·76); women on any antiretroviral therapy (0·05, p=0·63) or no therapy (−0·04, p=0·63); women with any genital infection (0·01, p=0·87) or no infection (−0·04, p=0·67).

Six (2%) women had very low concentrations of retinol (<0·70 μmol/L). In these individuals, we saw no association with quantity or detectability of CVL HIV-1 RNA (p=0·76 and 0·59, respectively), but the small numbers precluded meaningful analysis.

Our results accord with, and could help explain, those of another study,[3] which indicated no association between retinol status and perinatal HIV-1 transmission. By contrast with the findings of the African studies,[4,5] we saw no association between quantity or detectability of CVL HIV-1 RNA and retinol concentrations or retinol deficiency. Our results may differ from those of the African studies for several reasons.

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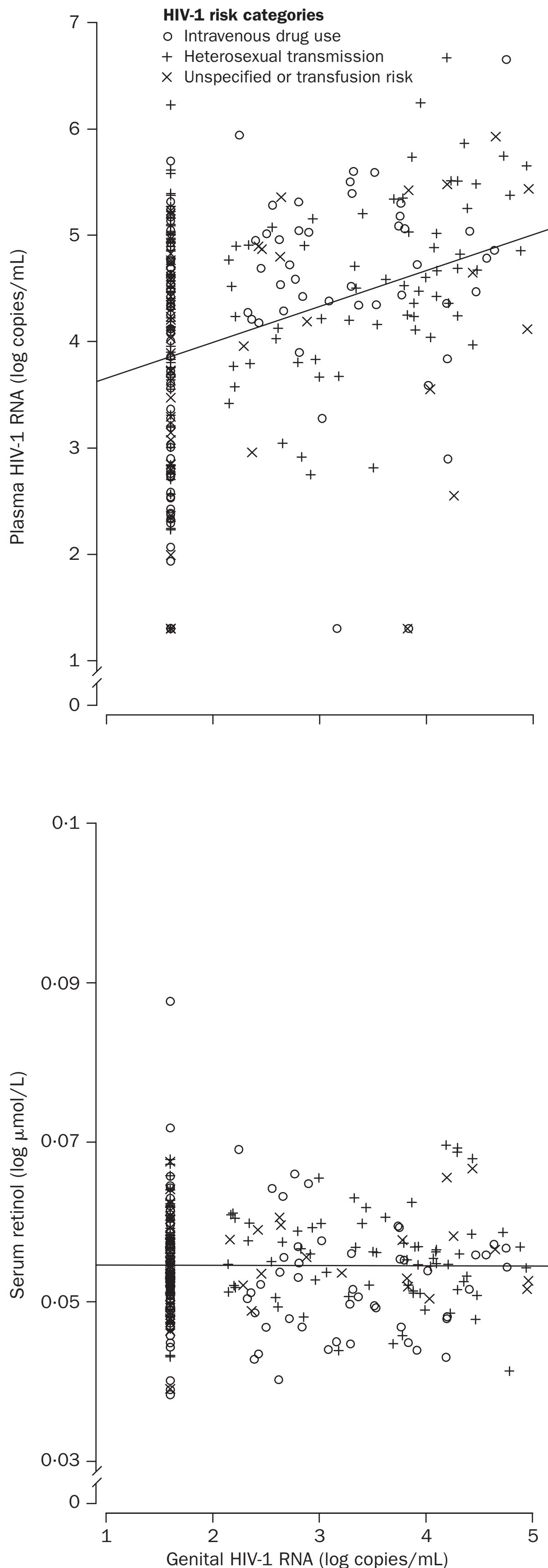

Correlation between plasma and genital HIV-1 RNA in 274 women (upper), and between serum concentration of retinol and genital HIV-1 RNA in 301 women (lower)

Retinol deficiency was more frequent and more severe in the African studies than in ours. The definition of retinol deficiency that we used has been used before,[2,5] but does not represent profound deficiency; women in our study might not have had deficiency severe enough to impair mucosal integrity. Results of the African studies show a relation between retinol deficiency and vaginal but not cervical HIV-1 DNA detection. Because the cervical and vaginal secretions were pooled in our study, we could not assess an effect of retinol deficiency on vaginal HIV-1 shedding. The difference in viral markers could have affected results—ie, HIV-1 DNA is detected in infected cells whereas RNA measures cell-free virus. Because retinol deficiency affects mucosal integrity, it could affect shedding of infected cells and not influence HIV-1 RNA concentrations.

Low serum retinol concentrations are linked to acute infections, malabsorption, and overall poor nutritional status.[3] The statistical associations seen between retinol deficiency and detectable vaginal HIV-1 DNA in the African studies might have been caused or exacerbated by an epidemiological or nutritional confounder not present in our population.

Although we can only postulate about the discrepancies between our study and others, the power of our analysis and the absence of any trend toward an association suggest that, in this population, a correlation between retinol status and genital HIV-1 burden does not exist.

Contributors

A L French and M H Cohen conceived and designed the study. A L French also prepared the report, coordinated retinol measurements, and analysed data. S J Gange did statistical analyses, H Burger and K Anastos helped with study design, W Gao helped with data collection, management, and analysis, R D Semba did retinol measurements and analysed results, W A Meyer measured HIV-1 viral load and interpreted the data, and E Robison designed the tools for data collection and obtained clinical data. All authors reviewed the final report.

Conflict of interest statement

None declared.

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