



Figure 2: Relation between prothrombin index, time since paracetamol ingestion, and treatment with acetylcysteine

variable. We excluded 15 patients whose time of paracetamol ingestion was unknown, which left 72 patients in the analysis. Each patient was entered three times into the analysis: at baseline and at the times of the next two prothrombin index measurements (figure 2). Mean time between the first and second entry was 7.4 h (6.3–8.5) and between the first and the third entry was 17.1 h (15.2–18.9). The decrease in the index value was strongly associated with the initiation of treatment (standardised correlation coefficient  $\beta = -0.69$  [ $-0.60$  to  $-0.78$ ]), whereas time since paracetamol ingestion was not ( $0.09$  [ $-0.03$  to  $0.20$ ]).

The initial decrease in the prothrombin index was consistently seen in patients with paracetamol poisoning without signs of hepatocellular injury. The time of decrease was strongly associated with the start of acetylcysteine infusion. A similar effect of acetylcysteine infusion on prothrombin concentrations has been described in patients with adult respiratory distress syndrome and in healthy people.<sup>3,4</sup> The mechanism behind the anticoagulant properties of acetylcysteine is unclear, but might be related to destabilisation of proteins, including clotting factors that contain disulphide bonds.<sup>5</sup> Thus, our findings could result from the effect of acetylcysteine on coagulation.

In the management of acute paracetamol poisoning, a fall in coagulation activity is generally thought to be a result of decreased synthesis of clotting factors, which is associated with the development of liver failure.<sup>2</sup> Since the indications for starting acetylcysteine treatment are broad, many patients receive treatment without ever developing signs of hepatocellular injury. Our results show that the decrease in prothrombin index values caused by acetylcysteine can be large and, consequently, could be misinterpreted as a sign of liver failure. Even though the prothrombin index provides useful prognostic information, management decisions should not solely be based on measurement of this value.

#### Contributors

F Bendtsen and K Dalhoff had the original idea for the study. L E Schmidt designed the study with contributions from all authors. L E Schmidt and T T Knudsen obtained data. L E Schmidt did data analysis and wrote the report with contributions from all authors.

#### Conflict of interest statement

None declared.

#### Acknowledgments

There was no funding source for this study.

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## Pre-eclampsia, antiretroviral therapy, and immune reconstitution

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**Antiretrovirals are standard treatment for HIV-1-positive women during pregnancy in the UK, but little is known about maternal or fetal safety. In our cohort study of 214 pregnant women with HIV-1 infection, those who received no antiretroviral therapy had a rate of pre-eclampsia significantly lower (none of 61) than those on triple antiretroviral therapy (8 of 76; odds ratio 15.3, 95% CI 0.9–270,  $p=0.0087$ ). However, the rate of pre-eclampsia in HIV-1-positive women on treatment did not differ from that in uninfected controls (12 of 214;  $p=0.2$ ). The association of HIV-1-related immune deficiency with a low rate of pre-eclampsia, and the restoration of this rate in women treated with triple antiretroviral therapy to the expected rate indicates a pivotal role of the immune system in the pathogenesis of pre-eclampsia. The clinical presentation of pre-eclampsia and toxic effects of antiretroviral therapy could overlap and complicate diagnosis and management in these patients.**

*Lancet* 2002; **360**: 1152–54

Mother-to-child transmission of HIV-1 in the UK has been greatly reduced since the introduction in 1994 of zidovudine monotherapy for pregnant women. However, recommendations state that advanced HIV-1 infection in pregnant women should be treated with combination antiretroviral therapy (ART), which through more complete suppression of viral replication allows greater and longer recovery of immune function than monotherapy.<sup>1</sup> However, there is little evidence for the safety of combination ART in pregnancy.

Between 1990 and 2001, we investigated the rate of pre-eclampsia in 214 women with HIV-1, who we monitored throughout their pregnancy at two London hospitals. These patients were group matched for age, parity, and ethnic origin with 214 HIV-1-negative women who delivered between 1998 and 2000, during which time the voluntary uptake of antenatal HIV-1 screening was greater than 90%.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (years)	39	30	35	38	38	34	30	25	33
Ethnic origin	African	African	African	African	White	African	African	African	African
Parity	2	3	1	2	0	0	0	0	2
Gestation (weeks)	30	37	31	38	38	35	24	26	31
Diagnosis	HELLP	HELLP	PET	PET	PET	PET IUD	HELLP IUD	PET IUD	HELLP
Blood pressure (mm Hg)									
At first appointment	100/60	100/70	100/70	125/75	110/60	120/80	120/70	110/70	100/60
Maximum	140/100	160/120	150/100	220/160	140/92	150/100	160/120	150/110	150/105
Proteinuria	Nil	3+	3+	2+	2+	Nil	3+	4+	2+
Platelets ( $\times 10^9/L$ )	86	48	81	493	230	199	115	175	70
Creatinine ( $\mu\text{mol/L}$ )	266	246	118	86	80	78	58	54	121
Alanine transaminase (IU/L)	133	178	19	56	10	56	75	14	41
CD4									
Pre-treatment*	110 (5)	70 (7)	10 (1)	540 (32)	150 (16)	n/a	323	401	n/a
At delivery*	170 (7)	110 (9)	70 (3)	430 (32)	370 (22)	360 (21)	339	401†	580 (24)
CD8									
Pretreatment*	1570 (69)	430 (43)	560 (61)	720 (43)	620 (51)	n/a	608	782	n/a
At delivery*	1540 (65)	540 (46)	1860 (77)	530 (40)	1090 (64)	800 (46)	755	782†	1320 (55)
HIV-1 RNA (copies/mL)									
Pretreatment	5258	7132	10098	3960	2026	n/a	61744	9105	n/a
At delivery	<400	<400	<50	3620	<50	<50	n/a	n/a	<50
Antiretrovirals									
NRTI	D4T ddl	D4T ddl	AZT 3TC	AZT	AZT 3TC	D4T ddl	AZT 3TC	AZT 3TC	AZT 3TC
NNRTI	Nev		Nev		Nev	Nev	Nev	Nev	
Protease inhibitors		Nelf							Nelf

NRTI=nucleoside analogue reverse transcriptase inhibitors. AZT=zidovudine. D4T=stavudine. ddl=didanosine. 3TC=lamivudine. NNRTI=non-nucleoside reverse transcriptase inhibitor. Nev=nevirapine. Nelf=nelfinavir. IUD=intrauterine death. HELLP=haemolysis, elevated liver enzymes, low platelets. PET=pre-eclampsia. n/a=not available. \*Absolute CD4 or CD8 lymphocyte count  $\times 10^6/L$  (% of total lymphocytes). †Patient presented after only 24 h on triple therapy. +refers to degree of proteinuria on urine dip stick test.

Table 1: Demographics, treatment, and outcome in HIV-1-positive women with pre-eclampsia

Women with pre-existing medical conditions such as renal disease were excluded. We used the definition of pre-eclampsia proposed by Higgins and de Swiet.<sup>2</sup> The HIV-1-positive cohort was stratified by treatment: untreated, mono (zidovudine) or dual ART (zidovudine plus lamivudine), and triple ART (consisting of a combination of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor). We analysed our findings with Fisher's exact test (incorporating the approximation of Woolf if the observed rate is 0).

Pre-eclampsia was diagnosed in nine HIV-1-positive women (table 1) and in 12 of 214 controls (6%). Ethnic origin, age, and parity did not differ between the cohorts (table 2). Within the HIV-1-positive cohort the rate of pre-eclampsia was significantly lower in women who were untreated (none of 61 who presented before 1994;  $p=0.0087$ ) or on mono or dual therapy (one of 77; 1%;  $p=0.018$ ) than in women who took triple ART (eight of 76, 11%) (table 1) (untreated—odds ratio 15.3, 95% CI 0.9–270; mono or dual therapy—8.9, 1.1–73). However, there was no significant difference in the rate of pre-eclampsia between women on mono or dual ART and the untreated HIV-1-positive group. Compared with the HIV-1-negative control cohort there was no significant difference in the rate of pre-eclampsia with triple ART ( $p=0.2$ ), or with mono or dual therapy ( $p=0.2$ ), but the lower rate of pre-eclampsia in the HIV-1-positive untreated group was of borderline significance ( $p=0.07$ , odds ratio 0.13, 95% CI 0.01–2.3).

Seven of the nine patients had unusually severe pre-eclampsia. Four had HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) and three had intrauterine deaths (table 1). Although pre-eclampsia has a low frequency in multiparous women without a previous episode of pre-eclampsia or a new partner, five of the nine women were multiparous, and only one had a new partner. Only patient 1 had a history of hypertension during a previous pregnancy. All nine women had contracted HIV-1

through heterosexual intercourse; none had chronic hepatitis B or C, or any history of intravenous drug use. Patients 1, 2, 3, 6, 7, and 9 had taken ART before their current pregnancy, whereas HIV-1 infection was newly diagnosed in the other three.

The apparent restoration of the rate of pre-eclampsia to that recorded in controls when HIV-1-positive women are treated with triple ART might be due to immune reconstitution induced by triple ART, or to an overlap in the clinical manifestations of the adverse effects of ART and pre-eclampsia, or both. One patient presented with hepatitis, pancreatitis, and hyperbilirubinaemia, and four others had abnormal liver function tests. These abnormalities have been reported in both the HELLP syndrome<sup>3</sup> and in patients on nucleoside analogue reverse transcriptase inhibitors.<sup>1</sup>

Lactic acidosis is a recognised complication of these drugs, but the deaths of three pregnant women who took stavudine with didanosine have raised concern that pregnant women could be more susceptible to this complication.<sup>4</sup> The prevalence of lactic acidosis related to nucleoside analogue reverse transcriptase inhibitors in pregnancy has not been reported, but in our cohort four (including three who had pre-eclampsia) of seven women treated with a regimen that

	Mono or dual therapy (n=77)	Triple ART (n=76)	Untreated (n=61)	Controls (n=214)
Age (years; median [range])	29 (20–40)	32 (21–37)	28 (23–36)	30 (20–40)
Ethnic groups n (%)				
African	64 (83.1%)	61 (80.2%)	49 (80.3%)	174 (81.3%)
White	12 (15.6%)	14 (19.5%)	12 (19.7%)	38 (17.8%)
Asian	1 (1.3%)	1 (1.3%)	0	2 (1%)
Parity n (%)				
Multiparous	51 (66.2%)	55 (72.4%)	42 (68.9%)	148 (69.1%)
Primiparous	26 (33.8%)	21 (27.6%)	19 (31.1%)	66 (30.9%)

Fisher's exact testing between the three cohorts showed no significant differences between the three cohorts for the parameters presented.

Table 2: Age, ethnic groups, and parity in the HIV-1-positive cohorts

contained stavudine and didanosine had evidence of lactic acidosis. Drug toxicity was suspected and treatment was discontinued in one of the three, although the initial presentation was typical of pre-eclampsia. Even when we excluded this case from the triple-therapy group, the low rate of pre-eclampsia compared with the untreated HIV-1-positive group remained significant ( $p=0.017$ ).

We therefore conclude that the immune restorative effect of triple ART might be implicated in development of pre-eclampsia. Evidence suggests that normal pregnancy is a pro-inflammatory state and that pre-eclampsia might be an exaggeration of this immune response. HIV-1 infection is characterised by a progressive loss of CD4+ lymphocyte activity. This immune suppression could explain the low frequency of pre-eclampsia in untreated HIV-1-positive women. Triple ART results in immune reconstitution. An initial increase in CD4+ and CD8+ memory cells is followed by a slower increase in naive CD4+ and CD8+ T cells, which are capable of responding to new antigens.

We propose that effective ART might restore the pregnant woman's immune response to fetal antigens, and hence could reinstate the pathological processes that result in pre-eclampsia. Pre-eclampsia may therefore be another manifestation of immune restoration, similar to the exacerbation of other immune-mediated diseases (viral hepatitis, cytomegalovirus retinitis, and disseminated mycobacterium) that follows effective ART. In other situations, immune reconstitution syndromes arise soon after ART is started, when the target antigen is abundant. However, this is not necessarily the case in pre-eclampsia, in which the effect of immune reconstitution is dependent on the timing of pregnancy rather than the timing of therapy.

Our results suggest that the compromised immune system in untreated HIV-1 infection is associated with reduced rate of pre-eclampsia. A similarly low rate (0.8%, five of 634 cases) has been recorded in a demographically comparable, predominantly untreated, HIV-1-positive cohort in the USA.<sup>5</sup> ART results in an increased incidence of pre-eclampsia dependent on the magnitude of immune reconstitution; triple therapy has a greater effect than mono or dual therapy. However, pre-eclampsia might be more severe and diagnosis more difficult in patients on triple therapy, because of the overlap between clinical signs of pre-eclampsia and adverse effects of ART.

Pregnant women on ART are increasingly common in inner city antenatal clinics in the UK, and vigilance for the complications of therapy and pregnancy should be increased. Our data provide evidence for the pivotal role of the immune system in the pathogenesis of pre-eclampsia.

#### Contributors

R C Wimalasundera and G P Taylor designed the study, obtained data, did statistical analysis, and drafted the report. J H Smith, N Larbalestier, and A de Ruiter provided clinical data. A D Hughes, S A McG Thom, L Regan, and N Poulter contributed to the writing and revisions of the letter.

#### Conflict of interest statement

None declared.

#### Acknowledgments

We thank midwives Cecilia Ward and Jane Kennedy for identification of the cases at St Mary's and St Thomas' Hospitals, and C L Chang for her invaluable statistical advice. R Wimalasundera was funded by a British Heart Foundation Junior Fellowship. The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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