

Survival and progression of HIV disease in women Attending GUM/HIV clinics in Britain and Ireland

Study Group for the MRC Collaborative Study of HIV Infection in Women*

Objectives: To describe the pattern of clinical disease in women with HIV infection and to examine the effect of potential cofactors, including oral contraceptive use, alcohol and smoking, clinic group, and route of HIV transmission, on progression to AIDS and death.

Design: Prospective observational cohort study.

Setting: 15 HIV and genitourinary medicine (GUM) clinics in Britain and Ireland.

Participants: 505 women aged over 18 years with a positive HIV antibody test entered the study between June 1992 and August 1995, with outcome data available for 503 women, and 1208 woman years of follow up to April 1996.

Main outcome measures: AIDS defining conditions, incidence of AIDS, and death.

Results: 120 women (24%) had AIDS at entry to the study. There were 99 incident AIDS cases and 132 deaths during 1208 woman years of follow up. *Pneumocystis carinii* pneumonia (PCP) was the commonest first AIDS defining condition in white women (31% of AIDS cases), followed by oesophageal candidiasis (19%) while tuberculosis was the most common first AIDS defining condition among black African women (24% of AIDS cases), followed by oesophageal candidiasis (19%). In multivariate analyses, rate of progression to AIDS was significantly related to CD4 lymphocyte count at entry and PCP prophylaxis, but not to ethnic group, route of HIV transmission, alcohol, smoking, or oral contraceptive use. Mortality from all causes was not significantly different in women infected through injecting drugs (adjusted ratio 1.1, 95% confidence interval 0.7-1.8) compared with those infected through sexual intercourse, and non-significantly lower in black African women (0.7, 0.3-1.2) compared with white women. Survival was not significantly related to smoking, alcohol, or oral contraceptive use.

Conclusions: In women attending GUM/HIV clinics, the pattern of AIDS defining conditions differs by ethnic group, but progression of HIV disease is not importantly related to smoking, alcohol, oral contraceptive use, route of HIV transmission, or ethnic group.

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Keywords: HIV infection; women; cohort study; survival; AIDS; ethnic group

Introduction

HIV infection in the United Kingdom was first diagnosed in well defined groups of homosexual men, injecting drug users (mostly male), and men with haemophilia, and progression of HIV infection has mostly been studied in these groups.¹⁻⁴ Subsequent spread of HIV to women has been rapid, with the proportion of infections diagnosed in women in the United Kingdom increasing from 9% in 1986 to 23% in 1997.⁵ The experience of other developed countries has been similar.⁶ In response to the rising epidemic in women, a few prospective studies⁷⁻¹¹ were set up in the late 1980s or early 1990s specifically to examine the course of HIV infection in women. We report on one such study, a prospective cohort of women attending genitourinary medicine (GUM)/HIV clinics in Britain and Ireland.¹² It was designed to describe the clinical presentation and progression of HIV infection in women.

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Increasing age and viral load, and low CD4 count are the only well established risk factors for progression of HIV disease in men or women.¹³⁻¹⁴ The role of other potential risk factors, such as ethnicity, route of transmission, and socioeconomic class, is less clear. Some studies have found that prognosis varies significantly in relation to such factors,⁸⁻¹¹ others have not.¹⁴⁻¹⁵ It has been suggested that access to health care may explain the differences between studies.⁸ Other modifiable factors, such as smoking and oral contraceptive use, might theoretically be linked to disease progression through their effects on CD4 levels.¹⁶ We describe here the effect of putative risk factors including ethnic group, route of HIV transmission, oral contraceptive use, alcohol, smoking, and socioeconomic class on progression of HIV disease in women receiving care at GUM/HIV clinics.

Methods

Sociodemographic and clinical characteristics of the women at entry to the cohort have been described elsewhere.¹² Briefly, women attending STD/GUM clinics who were HIV antibody positive, aged 18 or above and available for follow up were invited to take part in the study. Eighty eight per cent of women invited to enter the study agreed to do so and gave written informed consent. Five hundred and five women were recruited from 15 clinics between June 1992 and August 1995. Ten clinics were in London, one in Dublin, one in Edinburgh, and three in south east England. At each clinic, all women were interviewed by the local investigator (research nurse or physician). Data obtained through direct questioning and review of medical/laboratory records (for example, for details of AIDS defining diseases) were recorded by the investigator onto a standard study form. Data collected at entry to the study included ethnic group, occupation, likely route of exposure to HIV, past and current morbidity, including AIDS defining conditions, smoking and alcohol use, and gynaecological history. Ethnic group was self assigned and a hierarchical system was used to determine the probable route of transmission as previously described.¹²

A recruitment target of at least 400 women was set to provide sufficient incident AIDS cases (at least 70 over 3 years follow up, or 1200 woman years) for analysis of factors relating to HIV progression, assuming that the progression rate in women is similar to that in men with haemophilia.¹⁷ Local investigators aimed to follow up the women approximately every 6 months, or more frequently according to clinical need. At each follow up visit, clinical and drug histories were updated. Women were followed until date of death, or date of last follow up visit before 15 April 1996. Individual data on AIDS defining conditions and AIDS related deaths were verified by matching (using soundex codes) with national surveillance databases held at the Communicable Disease Surveillance Centre (CDSC).

STATISTICAL ANALYSIS

Comparisons of median values between the ethnic and transmission subgroups were done using standard non-parametric tests. (Kruskal-Wallis test). Comparisons between the proportions in these groups were done using the X^2 distribution. The influences of these factors on mortality and the development of AIDS defining diagnoses were examined using Cox proportional hazards model with time dependent covariates fitted using the PHREG procedure in SAS (Statistical Analyses System Inc, Cary, NC, USA). Enrolment date to the study was taken as time zero. Follow up of the women was censored at 15 April 1996, 1 year before the matching date with CDSC. Antiretroviral drug use and *Pneumocystis carinii* pneumonia (PCP) prophylaxis were fitted as time dependent covariates—that is, the start of either of these drugs was updated during the follow up period. Log CD4 at entry was fitted as a fixed variable to adjust for illness at entry to the study.

Results

Table 1 shows baseline characteristics of the women at entry to the study. There were three main ethnic/HIV transmission subgroups of approximately equal size: 30% (n=151) of the cohort were black African, of whom 93% were heterosexually infected, 33% (n=168) of the cohort were white women infected through shared drug injecting equipment, and 28% (n= 140) were white heterosexually infected

Tablet Baseline characteristics of the cohort, by ethnic/transmission subgroups

	<i>All women (n=505)</i>	<i>Black African (n=151)</i>	<i>White sexually infected(n=140)</i>	<i>White IDU (n=168)</i>	<i>p Value</i>
Median age ac study entry (years)	30 (25-39)*	29 (24-37)*	31 (25-43)*	30 (26-39)*	0.003
Median age at first HIV test (years)	26 (21-35)*	27 (22-35)*	27 (22-40)*	24 (19-32)*	0.0001
AIDS, n (%)	120 (24)	34 (24)	35 (25)	39 (23)	0.88
CD4 count <200 x10 ⁶ /l, n (%)†	191 (39)	71 (48)	49 (37)	56 (34)	0.02
Median CD4 count (x10 ⁶ /l)	270 (20-658)*	205 (20-580)*	312(10-690)*	285 (30-650)*	0.02
Symptom free, n (%)	314(65)	102 (69)	87 (64)	95 (60)	0.21
Current regular sexual partner, n (%)	280 (56)	77 (51)	83 (59)	96 (57)	0.36
Sexual partner in past 6 months, n (%)	301 (60)	85(57)	88 (63)	100 (61)	0.51
Median age at first sexual intercourse	17 (14-20)*	18 (15-21)	17 (14-21)*	16 (13-18)*	0.0001
Lifetime male sexual partners, n (%)					
0	3(1)	—	—	3 (2)	<0.0001
1	36(8)	11 (8)	10 (7)	9 (6)	
2-3	116(24)	56 (41)	17 (12)	38 (24)	
4-9	172 (36)	62 (45)	51 (37)	43 (27)	
>9	152 (32)	9 (7)	60 (44)	68 (42)	
Occupational status					
non-manual	237 (51)	69 (34)	84 (64)	60 (38)	<0.0001
manual	149 (32)	24 (19)	38 (29)	76 (48)	
student	20(4)	8(6)	4 (3)	5 (3)	
mother	56(12)	28 (22)	5 (4)	19 (12)	
Marital status					
married	96 (19)	26 (17)	28 (20)	28 (17)	0.0001
widowed	48 (10)	14(9)	21 (15)	9 (5)	
divorced	31(6)	2(1)	14 (10)	14(8)	
separated	52(10)	23(15)	4(3)	22 (13)	
single	275 (55)	85 (57)	73 (52)	93 (56)	
Ever on PCP prophylaxis, n (%)	182 (36)	70 (46)	42 (30)	56 (33)	0.01
Ever on anoretrovirals, n (%)	190 (38)	54 (36)	48 (34)	73 (43)	0.24
Cervical smear result‡					
normal	240 (61)	70 (57)	76 (59)	67 (62)	??
borderline/mild dyskaryosis	94 (24)	32 (26)	29 (23)	27 (25)	
moderate/severe dyskaryosis	25(6)	8(7)	9(7)	8(7)	
other, including unknown	35 (9)	12(10)	15(12)	6(6)	
Current smoking, n (%)	259 (51)	16(11)	74 (53)	150 (89)	<0.001
Current alcohol, n (%)	330 (66)	92 (61)	103 (74)	104 (62)	0.4
On oral contraceptives	73 (15)	26 (17)	15(11)	21 (13)	0.25
Centre					
Edinburgh	58 (12)	—	14(10)	41 (24)	<0.001
Dublin	84 (17)	1(1)	23 (16)	59 (35)	
London and SE England	363 (72)	150(99)	103 (74)	68 (41)	

*10th to 90th centile range; †16 values missing; ‡111 values missing.

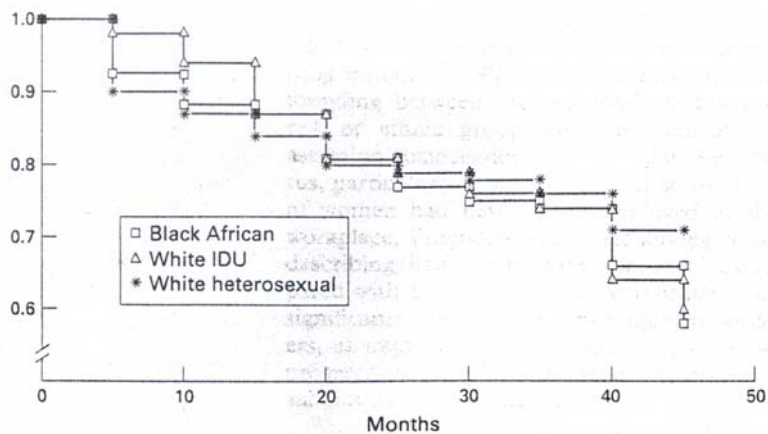


Figure 1 Probability of developing AIDS (from study entry to first AIDS diagnosis or last follow up) by ethnic/transmission subgroups.

women. The remaining women (9%) were of other or mixed ethnic group. All except one of the black African women were recruited from centres in London or south east England, whereas the injecting drug users were more evenly distributed across study centres.

The proportion of women with AIDS at entry was very similar across subgroups, although a significantly ($p=0.02$) higher proportion of black African women had CD4 counts below $200 \times 10^6/l$ at entry. Around two thirds of women in each subgroup were free of symptoms at study entry. Just over half of the women had a current regular sexual partner, but white women reported significantly more lifetime sexual partners and a lower age at first sexual intercourse than black African women. Just over half of the women in each subgroup were single, with around one fifth married; divorce was much less common in black African women than white women.

The proportion of women who had ever been on PCP prophylaxis was significantly higher among black African women than white women, which may reflect their lower CD4 counts. There was no significant difference in the proportions who had ever been on antiretroviral therapy. Around two thirds of women were current alcohol drinkers, with nonsignificant differences between subgroups, whereas there were big differences between subgroups in the proportion of current smokers (table 1). Reported levels of smoking and drinking were generally modest, with 40% of drinkers having less than 5 units per week and 75% of smokers reporting no more than three cigarettes per week.

FOLLOW UP

Outcome data were available for 503 (99.6%) of the 505 women. The two women for whom no follow up data were available had moved abroad shortly after entering the study. Four hundred and two women (80%) attended at least one follow up visit during the study.

The distribution of combined prevalent (at study entry) and incident first AIDS defining conditions differed by ethnic/transmission subgroup. (Detailed data are available from the journal office.) The most marked difference between subgroups is in occurrence of tuberculosis, which was the commonest first AIDS defining condition in black African women. Tuberculosis accounted for 24% of AIDS cases in black African women, but only 5% of cases among white women. PCP was the commonest first AIDS defining condition in both white subgroups, accounting for 37% of cases among sexually infected women and 26% among IDU. Oesophageal candidiasis was the second commonest AIDS defining condition in all subgroups, accounting for 15% to 23% of cases.

The most commonly diagnosed non-AIDS defining diseases were vaginal candidiasis (12.2% of all non-AIDS diagnoses), oral candidiasis (9.6%) widespread lymphadenopathy (7.6%), non-genital herpes simplex, nonspecific skin disorders (4.4%), genital herpes (4.4%), genital warts (3.9%), and hairy leucoplakia (3.7%). Hepatitis B and C and community acquired pneumonia were significantly

($p < 0.0005$) more common among injecting drug users (5.5%, 4.6%, and 4.5% respectively) than other subgroups (all less than 2%), but there were no other appreciable differences in the occurrence of common, non-AIDS defining conditions between ethnic/transmission subgroups (data not shown). During follow up, a total of 271 women took antiretroviral treatment, 81 for the first time. Of those on therapy, 133 (49%) took only zidovudine, 129 (48%) used another antiretroviral drug at some time in addition to zidovudine, and only nine (3%) women took other antiretrovirals alone.

A total of 297 women had at least one cervical smear during follow up: in 44 women (15%) the smear result deteriorated, in 31 (10%) it improved, in 13 (4%) it fluctuated, and in the remaining 70% it did not change.

In univariate analyses, progression from study entry to AIDS was significantly associated with taking antiretroviral therapy (crude hazard ratio 2.53, 95% confidence interval 1.70-3.75) or PCP prophylaxis (hazard ratio 4.88, 95% CI 3.25-7.33) and infection via blood products (3.81, 1.38-10.55) and inversely related to log CD4 count (0.37, 0.31-0.43). In multivariate analyses, only log CD4 (adjusted hazard ratio 0.41, 95% CI 0.33-0.51) and PCP prophylaxis (2.19, 1.25-3.82) remained significantly related to progression to AIDS, after adjustment for age and centre effect. With all cause mortality as the end point, the findings were similar. In the multivariate model, survival was significantly related to infection via blood transfusion/ products (adjusted hazard ratio 3.14, 95% CI 1.33-7.39) and PCP prophylaxis (4.43, 2.6-7.5) as well as log CD4 count (0.59, 0.51-0.68) and AIDS at entry (2.36, 1.54-3.72).

Smoking and alcohol, whether fitted as categorical or continuous variables, were not significantly related to progression or survival, nor was current use of oral contraceptives. Adjusted hazard ratio for smokers compared with non-smokers was 1.36 (0.75-2.45) for progression to AIDS and 1.72

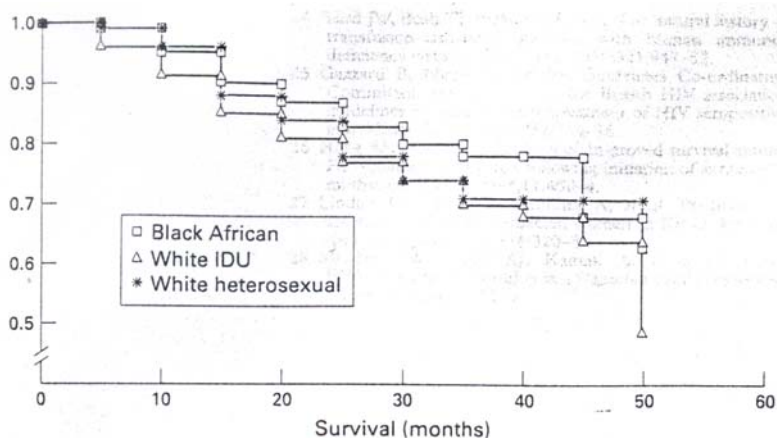


Figure 2 Probability of survival (from study entry to death or last follow up) by ethnic/transmission subgroups.

(0.99-2.99) for all cause mortality. Adjusted hazard ratio for drinkers compared with non-drinkers was 1.21 (0.73-2.00) for progression to AIDS and 0.66 (0.44-0.99) for all cause mortality. Adjusted hazard ratios for oral contraceptive pill users was 0.84 (0.42-1.66) for progression to AIDS and 1.01 (0.56-1.85) for mortality. Detailed results of analysis of potential cofactors in relation to progression to AIDS and survival are available in the journal office.

Figures 1 and 2 show similar survival curves for women in the three ethnic/transmission subgroups.

Discussion

The number of reported HIV infections in women in the United Kingdom increased rapidly during the late 1980s and early 1990s, and is continuing to rise steadily. By September 1998, over 5120 cases of HIV infection and over 1660 cases of AIDS had been reported in women in the United Kingdom.³ As the impact of the epidemic on women increased, it became clear that research specifically focusing on women and HIV infection was much needed.¹⁸ There are still relatively few large prospective cohorts of women with HIV infection.⁸⁻¹⁰ Earlier cohorts have focused on more readily identified populations such as predominantly white homosexual men and injecting drug users,¹⁻³ often in a single city. In comparison with these populations, women with HIV are a less easily identifiable or socially cohesive group.

Our study is the largest multicentre cohort of women with HIV in the British Isles. We have previously described the socioepidemiological characteristics of this cohort and their uptake of medical interventions at baseline.¹² This paper presents prospective analyses of the effect of those factors on progression to AIDS and death. The pattern of first AIDS defining and other conditions in this cohort are very similar to comparable, large female cohorts, with PCP, oesophageal candidiasis, and wasting syndrome being the most common,⁸ except for black African women, in whom tuberculosis was the most common first AIDS defining diagnosis.²⁰ There was an increased prevalence of cervical abnormalities at baseline (6-7% of smears taken each year-in the United Kingdom show borderline or mild abnormalities, compared with 24% in this cohort). Other studies have reported similar findings.²¹

As expected, progression of HIV disease was most strongly related to clinical and immunological stage, indicated by a low CD4 count, AIDS diagnosis, or history of PCP prophylaxis at entry to the study. We found little difference in progression to AIDS or death between women infected through heterosexual intercourse, and those infected through injecting drug use. Most other prospective cohorts that have included women with HIV infection have not reported major survival differences related to mode of transmission,^{3,15,22,23} although some studies had relatively few women. In our study, progression to death, but not AIDS, was related to infection through blood transfusion/needlestick injury. Early studies suggested that people infected through blood exposure might receive a larger inoculum of virus than those infected via other routes.²⁴ With more widespread screening of blood transfusions over time, this has become a less important route of transmission, and the wide confidence limits around the odds ratios in our study reflect the small number of women (12) in this category.

Recent developments in antiretroviral therapy have had a major impact on the management and survival of people with HIV infection.^{25,26} This study predates the introduction of protease inhibitors and potent combination antiretroviral therapy. And the increased univariate hazard ratios associated with taking antiretroviral therapy reflects women with later stage disease being more likely to be on therapy, as it is reversed after adjustment for CD4 count. However, the increased hazard ratios associated with PCP prophylaxis persisted after such adjustment. This effect has been observed by others (Amanda Mocroft, personal communication) and may be explained by women being started on PCP prophylaxis in response to symptoms heralding the imminent diagnosis of PCP.

Several studies have looked at the relation between ethnic group or race and progression of HIV disease with conflicting results. Rapid progression to symptomatic disease among HIV infected Africans has been described,^{27,28} but studies in the United States have not found large differences in progression rates between black and white Americans after adjustment for access to health care.^{15,22} The question has recently been addressed in a retrospective cohort study of HIV infected Africans and non-Africans attending the same clinics in London.²⁰ Neither progression to AIDS nor death was significantly different between Africans and non-Africans after adjustment for age and clinical and immunological status at baseline. Our findings are similar, and support the view that ethnic differences are more likely to reflect differential access to care than inherent ethnic or racial differences in disease progression.

A few studies have attempted to examine the effect of socioeconomic status on disease progression.^{15,22,29} Problems here relate to confounding between socioeconomic status and risk or

ethnic group, and the difficulty of assigning socioeconomic or occupational status, particularly in women. In our study, 16% of women had never been employed in the workplace. Prognosis was worst among those describing their occupation as “mother.” Compared with this group, all cause mortality was significantly lower among non-manual workers, as might be expected, but differences in progression to AIDS between occupational subgroups were not significant.

Women who smoke have higher CD4 levels than women who do not smoke, while oral contraceptive use is associated with lower levels of CD4.¹⁶ We therefore examined the effect of these factors, plus alcohol intake, on disease progression. Drinking and/or smoking were frequently reported in this cohort, except by black African women, who were unlikely to smoke. The levels of intake were generally modest. We found no important relation between either smoking or alcohol and progression of HIV disease, although the confidence intervals are not narrow enough to exclude this possibility. Other, predominantly male, cohort studies have similarly reported no important differences between smokers and non-smokers in the overall risk of progression.^{30,31} There are few other data on the effect of alcohol intake on HIV disease progression in women.³²

We found no differences in disease progression between women currently taking the oral contraceptive pill and those using other or no form of contraception. One study has tentatively reported a protective effect of hormone replacement therapy on progression of HIV disease in older women (aged 40-75 years),³²-but we are not aware of other published cohorts that have examined the effect of hormonal contraceptives on HIV disease progression. Most research in this area has examined whether there is an association between hormonal contraception and risk of HIV transmission to women, or the amount of viral shedding in women with HIV infection.³³

In conclusion, this prospective study of women with HIV infection attending GUM/ HIV clinics in Britain and Ireland shows clear differences in the pattern of AIDS defining conditions between white and black African women, but no important differences in progression of HIV disease by smoking, alcohol, oral contraceptive use, ethnicity, or route of HIV transmission.

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GUM Shield football team (captain: Colm O'Mahony) taking part in competition held during MSSVD Spring Meeting in Llandudno. For report of meeting see News p 272.