

# Frequency of Gynecologic Follow-Up and Cervical Cancer Screening in the Swiss HIV Cohort Study

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**Background:** According to current recommendations, HIV-infected women should have at least 1 gynecologic examination per year.

**Objectives:** To analyze factors associated with frequency of gynecologic follow-up and cervical cancer screening among HIV-infected women followed in the Swiss HIV Cohort Study (SHCS).

**Methods:** Half-yearly questionnaires between April 2001 and December 2004. At every follow-up visit, the women were asked if they had had a gynecologic examination and a cervical smear since their last visit. Longitudinal models were fitted with these variables as outcomes.

**Results:** A total of 2186 women were included in the analysis. Of the 1146 women with complete follow-up in the SHCS, 35.3% had a gynecologic examination in each time period, whereas 7.4% had never gone to a gynecologist. Factors associated with a poor gynecologic follow-up were older age, nonwhite ethnicity, less education, underweight, obesity, being sexually inactive, intravenous drug use, smoking, having a private infectious disease specialist as a care provider, HIV viral load <400 copies/mL, and no previous

cervical dysplasia. No association was seen for living alone, CD4 cell count, and positive serology for syphilis.

**Conclusions:** Gynecologic care among well-followed HIV-positive women is poor and needs to be improved.

**Key Words:** cervical dysplasia, gynecology, HIV, Papanicolaou smear, women

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Gynecologic diseases are more frequent in HIV-infected women and are generally more severe.<sup>1–4</sup> Among the most frequent problems are vulvovaginal candidiasis and cervical dysplasia. Other sexually transmitted diseases, pelvic inflammatory disease, genital ulcer disease, and menstrual abnormalities are also common, however.<sup>2</sup>

HIV-infected women thus benefit greatly from routine gynecologic examinations, including a Papanicolaou smear for the screening of cervical dysplasia and cancer. Several guidelines have been elaborated with this purpose.<sup>5–8</sup> The common denominator in the different guidelines is at least 1 annual gynecologic examination, including a Papanicolaou smear.

The primary aim of our study was to analyze whether the recommendation for at least 1 annual gynecologic examination, including a Papanicolaou smear, in HIV-positive women was followed in Switzerland and to identify factors associated with poor compliance. Further, we wanted to analyze if the implementation of questionnaires led to an increase in gynecologic visits.

## METHODS

### Patients

The prospective Swiss HIV Cohort Study (SHCS) follows HIV-infected individuals aged 16 years or older who attended 7 outpatient clinics specialized in infectious diseases or affiliated outpatient clinics or were seen by private physicians. It was approved by the local ethical review boards. Written informed consent was obtained from all participants. Twice a year, information on demography, HIV-associated diseases, medications, and laboratory parameters is collected. A questionnaire was introduced in April 2001 asking specifically about gynecologic visits since the last follow-up visit and whether a cervical smear had been done.

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Women with at least 1 completed gynecologic questionnaire between April 1, 2001 and December 31, 2004 were included in the study.

### Statistical Analysis

The Pearson  $\chi^2$  test, Wilcoxon rank sum test, and a test for trend across ordered groups were used for the descriptive analysis. In addition, we performed multivariate longitudinal analyses in which the primary outcomes were “gynecologic visit” and Papanicolaou smear during a defined time period of 15 months. The 15-month time span was chosen because most of the study participants had 2 SHCS follow-up visits within 15 months and 2 follow-up visits were needed to assess whether the women had at least 1 yearly gynecologic visit. Therefore, the entire period during which the questionnaires were used was divided into 3 blocks of 15 months (April 1, 2001–June 30, 2002; July 1, 2002–September 30, 2003; and October 1, 2003–December 31, 2004).

The analysis was conducted using longitudinal generalized estimating equations (GEEs)<sup>9</sup> with a logit link and an exchangeable correlation structure. The explanatory variables included age at baseline, ethnicity (white vs. other), education (higher vs. lower, where the latter means not completed or just mandatory school), body mass index (BMI; <18.5 kg/m<sup>2</sup> [underweight], 18.5–25 kg/m<sup>2</sup> [recommended weight], 25–35 kg/m<sup>2</sup> [overweight and obesity class I], and >35 kg/m<sup>2</sup> [obesity class II and III]), living alone, being sexually active, current intravenous drug use, current smoker, baseline follow-up in an SHCS clinic or with a private physician, CD4 cell count, HIV viral load <400 copies/mL, previous cervical dysplasia, and the syphilis marker *Treponema pallidum* haemagglutination assay (TPHA). To adjust for a potential correlation of patients within the same center, we also fitted a multilevel mixed effect model with the center as a random effect.

Because some patients had only 1 SHCS follow-up visit in a time period, underreporting of gynecologic visits might have occurred. We have therefore performed a sensitivity analysis that includes only time periods with 2 visits. Estimates of associations were presented as odds ratios and 95% Wald confidence intervals.

A possible change in the proportion of patients who did not follow the recommendations was analyzed as the normal longitudinal approach, including the main predictor variable “time since introduction of the questionnaire.” All statistical analyses were conducted using STATA version 8.2 for Windows (Stata, College Station, TX).

## RESULTS

### Patient Characteristics

From April 1, 2001 to December 31, 2004, 2239 women had at least 1 follow-up visit in the SHCS, resulting in a total of 11,346 follow-up visits. Fifty-three women were excluded from the analysis because no questionnaire had been completed. The patient characteristics are shown in Table 1. For the 53 women excluded from the analysis, ethnicity was more often not known, the proportion of intravenous drug users was higher, and they had a shorter follow-up time. There were no differences for any of the other characteristics studied.

A gynecologic examination was reported on 4594 (44.6%) of the 10,302 SHCS follow-up visits. According to the patients, no abnormality was detected in 76% of the visits, the women reported a problem in 22% of visits, and the women did not remember in 2% of visits. The median number of SHCS follow-up visits was 6 (interquartile range [IQR]: 3–7 visits), and the median number of reported gynecologic visits was 2 (IQR: 1–3 visits). From the 4594 reported gynecologic visits, 3761 (82%) women reported a Papanicolaou smear, 330 (7%) did not, it was not possible (eg, after hysterectomy) for 75 (2%), and the women did not remember if they had had a Papanicolaou smear or this information was missing in 428 (9%) cases.

A total of 1146 (52.4%) women were followed over the entire study period ( $\geq 2$  SHCS visits in each of the 3 time periods). Among these, 7.4% had never had a gynecologic examination, 57.3% reported an examination at 1 or 2 of the time periods, and the remaining 35.3% reported a gynecologic examination in every time period. With a Papanicolaou smear as the outcome, the corresponding proportions are 12.5%, 61.6%, and 25.9%.

There were significant differences among the 7 study sites ( $P < 0.001$ ). The proportion of women who have never gone to a gynecologist varied between 2.7% and 14.1%, and the proportion with examinations reported in every time period varied between 18.5% and 59.4%. This center dependence was also confirmed in the multivariate model.

Table 2 shows the patient characteristics by response pattern.

### Longitudinal Analysis

The results of these analyses are shown in Figure 1. Common predictors for fewer gynecologic examinations and Papanicolaou smears are older age, nonwhite ethnicity, less education, underweight, obesity, current intravenous drug use, current smoker, being followed by an infectious disease specialist in private practice, and no previous dysplasia. The results of the sensitivity analysis were similar, except that no significant association was found for ethnicity and intravenous drug use. In addition, women with lower CD4 cell counts were less likely to have had a gynecologic examination.

### Change Over Time

The proportion of gynecologic examinations during the defined time periods remained constant: 70.3% between April 2001 and June 2002, 68.4% between July 2002 and September 2003, and 69.8% between October 2003 and December 2004. The absence of a time trend was also confirmed in the multivariate analysis (results not shown).

## DISCUSSION

This study is consistent with previous reports from the United States demonstrating that HIV-infected women often fail to receive necessary gynecologic care.<sup>10,11</sup> The fact that some reported no gynecologic care during the period studied (>3 years), despite evidence from an SHCS study showing that the incidence rate of cervical cancer in HIV-infected women is 8-fold compared with the general Swiss population,

**TABLE 1.** Baseline Characteristics of Study Participants and of Women Not Included in the Study

	<b>A: All Study Participants (n = 2186)</b>	<b>B: Women Followed by Infectious Disease Specialist Over Whole Study Period* (n = 1146)</b>	<b>P A Versus B</b>	<b>C: Women Not Included† (n = 53)</b>	<b>P A Versus C</b>
Median age (IQR), years	36 (32–41)	37 (33–42)	0.001	35 (32–41)	0.81
Ethnicity (n, %)					
White	1458 (66.7%)	824 (71.9%)	0.001	29 (54.7%)	<0.001
Nonwhite	702 (32.2%)	320 (27.9%)		14 (26.4%)	
Unknown	26 (1.1%)	2 (0.2%)		10 (18.9%)	
Education					
Higher	1138 (52.1%)	647 (56.5%)	0.02	28 (52.8%)	0.91
Lower	1048 (47.9%)	499 (43.5%)		25 (47.2%)	
BMI (kg/m <sup>2</sup> )					
<18.5	263 (12.0%)	128 (11.2%)	0.40	6 (11.3%)	0.13
18.5–24	1471 (67.3%)	795 (69.4%)		30 (56.6%)	
25–35	426 (19.5%)	215 (18.8%)		17 (32.1%)	
>35	26 (1.2%)	8 (0.7%)		0 (0%)	
Patient living alone	642 (29.4%)	343 (30.0%)	0.74	16 (30.2%)	0.69
Sexually active at baseline	1364 (62.4%)	731 (63.8%)	0.43	29 (54.7%)	0.26
Injection of illegal drugs at baseline	152 (7.0%)	43 (3.8%)	<0.001	9 (17.0%)	0.01
Current smoker	1156 (52.9%)	592 (51.7%)	0.50	26 (49.1%)	0.58
Treating infectious disease specialist in SHCS hospital	1513 (69.2%)	779 (68.0%)	0.49	40 (75.5%)	0.47
Other outpatient clinic and private practice	673 (30.8%)	367 (32.0%)		13 (24.5%)	
Baseline CD4 cell count (IQR), cells/μL	410 (261–613)	446 (290–654)	0.001	412 (214–544)	0.53
HIV viral load values <400 copies/mL at baseline (n, %)	1139 (52.1%)	714 (62.3%)	<0.001	22 (41.5%)	0.13
Previous cervical dysplasia	187 (8.6%)	119 (10.4%)	0.08	4 (7.6%)	0.80
TPHA syphilis marker positive	123 (5.6%)	65 (5.7%)	0.96	5 (9.4%)	0.24
Duration of follow-up since registration in SHCS (median, IQR), years	6.3 (3.0–10.1)	7.7 (5.2–12.1)	<0.001	4.1 (1.2–8.6)	0.002
On antiretroviral treatment at baseline (n, %)	1021 (46.7%)	625 (54.5%)	<0.001	30 (56.6%)	0.15

\*2 follow-up visits in every time period.

†Women were excluded if no gynecologic questionnaire was filled out.

is worrisome.<sup>12</sup> This has important clinical and public health implications, because gynecologic diseases may be missed or diagnosed at a late stage, where treatment becomes more difficult. Extension of this problem to the Swiss population, where health care is available to all, is of note, because inability to pay is presumably not an explanation for the problem. The compulsory health insurance covers the costs of gynecologic screening irrespective of the location of the care provider. The insured has to pay only a moderate contribution.

In the SHCS, obese or underweight women, those who smoke, and those with less education are less likely to see a gynecologist, confirming previous findings.<sup>13</sup>

The association of obesity with lack of care could be attributable to patient embarrassment or to a provider's reluctance to perform pelvic examinations.<sup>14</sup> Obesity and smoking have been shown to be risk factors for cervical dysplasia and cancer.<sup>15,16</sup> Therefore, the association between obesity, smoking, and lack of care is of special concern.

Underweight is a negative prognostic factor in HIV-infected people<sup>17,18</sup> and has multiple causes. Some of them (eg, anxiety, depression, gastrointestinal disturbances, or severe opportunistic diseases) may prevent regular gynecologic visits.

The association with less education might reflect a lack of patient knowledge about the benefits of regular care or the inability of unskilled patients to obtain needed care.<sup>19</sup> Smokers are probably less health conscious in general, and this might also explain why smoking was associated with less frequent gynecologic examinations.

Our results confirm that nonwhites are less likely to seek medical care.<sup>20,21</sup> A previous study from the SHCS showed that taking antiretroviral therapy and disease progression were not different among patients of different ethnic groups, however.<sup>22</sup> Nevertheless, the situation might be different for specific types of medical care. Differences may be explained by cultural barriers and by a possible lack of knowledge among nonwhite women,<sup>19</sup> thus, again, proceeding in parallel with educational level.

In a previous study,<sup>10</sup> no relation was found for intravenous drug use, whereas this remained significant in our study, even after adjusting for smoking. We believe that this difference is related to the large number of women included in our study. Intravenous drug users are probably less interested in medical problems other than those directly related to their HIV infection and their addiction.

**TABLE 2.** Patient Characteristics and Diagnosis of Cervical Dysplasia and Vulvovaginal Candidiasis According to Frequency of Gynecologic Examinations: Those Who Never Had a Gynecologic Examination, Those Who Sometimes Reported a Gynecologic Examination (ie, gynecologic examination in 1 or 2 of the 3 time periods), and Those Who Always Reported a Gynecologic Examination (ie, gynecologic examination in all 3 time periods)

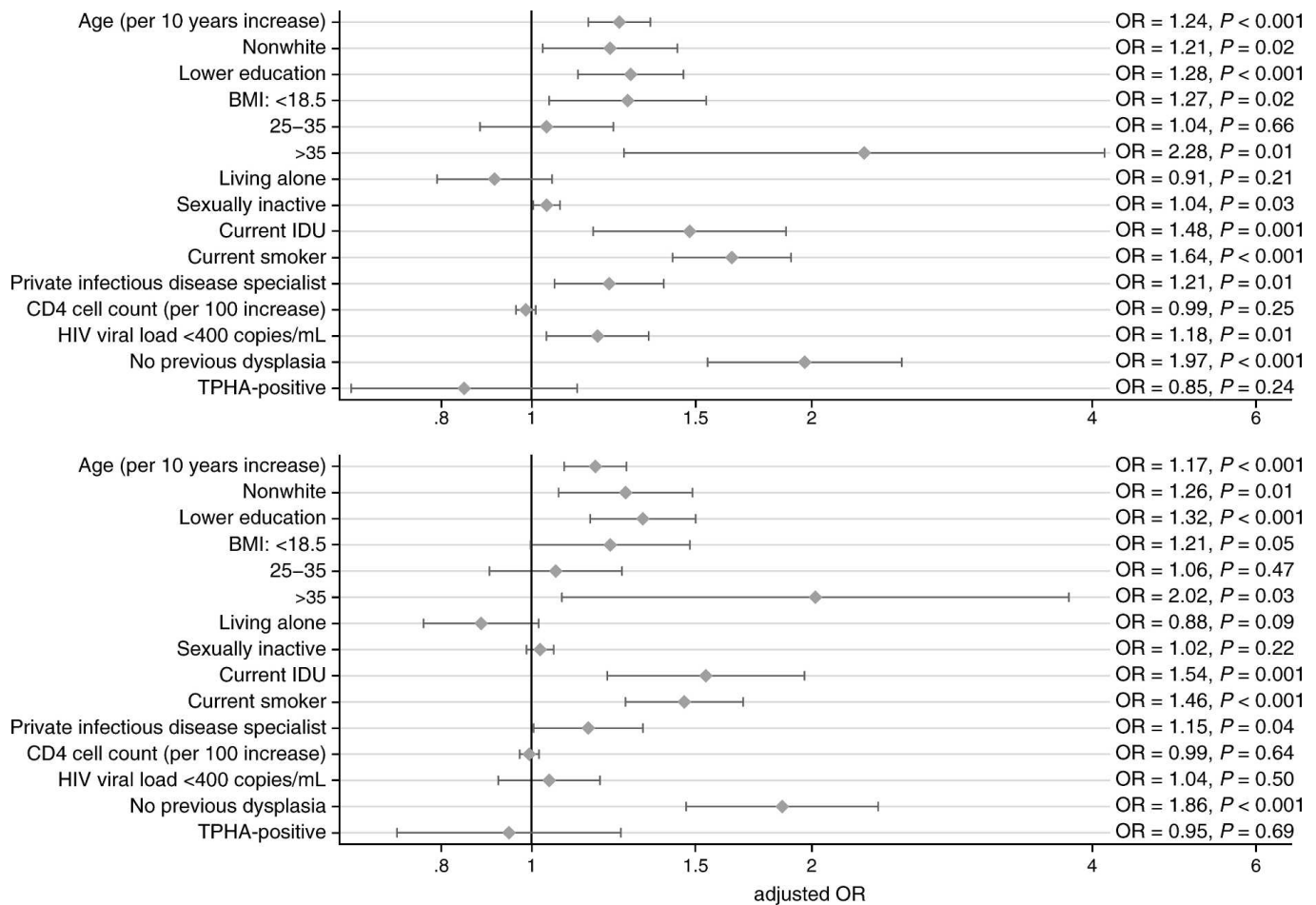
	Report of Gynecologic Examination			P
	Never (n = 85)	Sometimes (n = 657)	Always (n = 404)	
Median age (IQR), years	40 (37–45)	37 (33–42)	37 (33–40)	<0.001
Ethnicity (n, %)				
White	68 (80.0%)	471 (71.7%)	285 (70.5%)	0.17
Nonwhite	17 (20.0%)	185 (28.2%)	118 (29.2%)	
Unknown	0	1 (0.1%)	1 (0.2%)	
Education				
Higher	40 (47.1%)	353 (53.7%)	254 (62.9%)	0.001
Lower	45 (52.9%)	304 (46.3%)	150 (37.1%)	
BMI (kg/m <sup>2</sup> )				
<18.5	11 (12.9%)	85 (12.9%)	32 (7.9%)	0.56
18.5–24	59 (69.4%)	447 (68.0%)	289 (71.5%)	
25–35	15 (17.7%)	118 (18.0%)	82 (20.3%)	
>35	0	7 (1.1%)	1 (0.3%)	
Patient living alone (n, %)	31 (36.5%)	196 (29.8%)	116 (28.7%)	0.25
Sexually active at baseline	45 (52.9%)	419 (63.8%)	267 (66.1%)	0.05
Injection of illegal drugs at baseline	3 (3.5%)	31 (4.7%)	9 (2.2%)	0.12
Current smoker	54 (63.5%)	350 (53.3%)	188 (46.5%)	0.002
Treating infectious disease specialist in SHCS hospital	52 (61.2%)	439 (66.8%)	288 (71.3%)	0.05
Other outpatient clinic and private practice	33 (38.8%)	218 (33.2%)	116 (28.7%)	
Median baseline CD4 cell count (IQR), cells/μL	339 (237–530)	429 (285–657)	478 (322–679)	<0.001
HIV viral load values <400 copies/mL at baseline (n, %)	60 (70.6%)	403 (61.3%)	251 (62.1%)	0.42
TPHA syphilis marker positive	7 (8.2%)	36 (5.5%)	22 (5.5%)	0.50
Duration of follow-up since registration in SHCS (median, IQR), years	9.5 (5.5–13.7)	7.5 (5.2–11.3)	7.9 (5.2–12.6)	0.86
On antiretroviral treatment at baseline (n, %)	49 (57.7%)	343 (52.2%)	233 (57.7%)	0.31
No. women with a diagnosis of cervical dysplasia before this study (n, %)	3 (3.5%)	57 (8.7%)	59 (14.6%)	<0.001
No. women with a diagnosis of cervical dysplasia during this study (n, %)	0	18 (2.7%)	15 (3.7%)	0.08
No. women with a diagnosis of cervical cancer before or during study (n, %)	0	12 (1.8%)	6 (1.5%)	0.69
No. women with a diagnosis of vulvovaginal candidiasis before this study (n, %)	1 (1.2%)	38 (5.8%)	33 (8.2%)	0.01
No. women with a diagnosis of vulvovaginal candidiasis during this study (n, %)	0	12 (1.8%)	6 (1.5%)	0.69

Only patients who were followed over the whole study period of 45 months in the SHCS are included (n = 1146). The P value is based on a test for trend.

The association with low viral load is surprising. Women with low viremia tend to be more compliant to antiretroviral therapy, suggesting a better adherence to other recommendations as well. Feeling relatively healthy, these women may think that gynecologic visits are not too important or they might spend less time discussing health problems with their infectious disease specialist.

The center dependence and the association of poor gynecologic care and a private infectious disease specialist do suggest a problem with the health care system. A short ad hoc questionnaire to the treating infectious disease specialists has shown that communication between physicians seems to be easier in hospitals (ie, they more often get copies of the screening results) and that the proportion of patients who are referred to the gynecologists varies among centers.

Nonadherence to the recommended gynecologic examinations is a general problem and is not limited to the HIV population. Many factors associated with nonadherence found in our study have been described for women who were presumably HIV-negative.<sup>23</sup> Other factors were related to the patient's or physician's attitude (eg, woman's perception of importance of early detection, fear of abnormal results or difficulty of coping with them, physician's opinion about Papanicolaou smear) or to the system (eg, lack of time because of child care commitments or inconvenient opening hours, male gynecologist, poor communication regarding appointments, lack of social or instrumental support). We did not have this information in our study, because women were not asked about the reasons for not going to the gynecologist.



**FIGURE 1.** Association between no gynecologic examination or cervical smear during a time period of 15 months and predictor variables in the SHCS. Top, Model with a gynecologic examination as the outcome (n = 2186 patients). Bottom, Model with a cervical smear as the outcome (n = 2117 patients). Patients for whom no cervical smear was possible were excluded from the analysis. Less education corresponds to no completed or mandatory school. The reference category for the BMI is 18.5 to 25. IDU indicates intravenous drug use; OR, odds ratio.

Using a Papanicolaou smear instead of a gynecologic examination as the outcome, the results were similar. This is not surprising, because more than 80% of the gynecologic visits included a Papanicolaou smear.

In the sensitivity analysis, we excluded time periods with incomplete follow-up. The results obtained in this analysis were comparable to those obtained using all time periods. Despite the trend found, no significance was seen for nonwhite ethnicity, being sexually inactive, and intravenous drug use (probably because of the smaller sample size). Lower CD4 cell counts were associated with less frequent gynecologic examination visits in the sensitivity analysis only. This stands in contrast to the fact that immune-compromised women seek infectious disease specialists more often.

**Change Over Time**

The implementation of a questionnaire had no impact on the frequency of gynecologic visits, implying that other actions must be envisaged to improve adherence.

**Frequency of Gynecologic Diseases**

Fewer gynecologic examinations were associated with fewer diagnoses of cervical dysplasia and other relevant gynecologic diseases (see Table 2). In this study, it was not possible to establish causality, however, because no information on past gynecologic examinations was available.

**Limitations**

First, this questionnaire was based on the patient’s capacity for remembering/willingness to report during an interview with the individual’s physician or nurse, and reporting differences among patient groups may bias the results. Previous studies have shown overreporting of self-reported Papanicolaou smears.<sup>24-26</sup> They have asked about cervical smears within longer time periods, however, and the recall bias may thus be higher. Looking at general gynecologic examinations instead of Papanicolaou smears, the reporting accuracy was higher.<sup>26</sup> If overreporting existed, even more women would have inadequate gynecologic care.

Second, information on why women did not see a gynecologist, why they missed appointments, and the exact frequency of gynecologic examinations could not be addressed because of a lack of documentation in the SHCS.

Third, the results cannot be readily generalized to HIV-infected women outside the SHCS, although the SHCS reflects the general Swiss HIV population well.<sup>27</sup>

Fourth, some differences were found between the women for whom a questionnaire had been completed and those for whom it was not (see Table 1). Because of the high rate of completed questionnaires, however, there is little concern that this would affect the results.

## CONCLUSION

Gynecologic care among HIV-positive women followed in the SHCS is not satisfactory even though all these women were followed by an infectious disease specialist. If gynecologic care does not occur, the treating physician should try to elucidate possible reasons and explain to patients why this care is so important. This could be achieved using telephone counseling, educational or motivational brochures, and appointment reminders. The infectious disease specialist could also more often refer patients (at risk) to the gynecologist.

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