

HIV OR HIV-THERAPY? CAUSAL ATTRIBUTIONS OF SYMPTOMS AND THEIR IMPACT ON TREATMENT DECISIONS AMONG WOMEN AND MEN WITH HIV

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Abstract

Objectives: Among people with HIV, we examined symptom attribution to HIV or HIV-therapy, awareness of potential side effects and discontinuation of treatment, as well as sex/gender differences.

Methods: HIV-patients (N = 168, 46% female) completed a comprehensive symptom checklist (attributing each endorsed symptom to HIV, HIV-therapy, or other causes), reported reasons for treatment discontinuations and potential ART-related laboratory abnormalities.

Results: Main symptom areas were fatigue/sleep/energy, depression/mood, lipodystrophy, and gastrointestinal, dermatological, and neurological problems.

Top HIV-attributed symptoms were lack of stamina/energy in both genders, night sweats, depression, mood swings in women; and fatigue, lethargy, difficulties concentrating in men. Women attributed symptoms less frequently to HIV than men, particularly fatigue ($p < .01$).

Top treatment-attributed symptoms were lipodystrophy and gastrointestinal problems in both genders. Symptom attribution to HIV-therapy did not differ between genders.

Over the past six months, 22% switched/interrupted ART due to side effects. In women, side effect-related treatment decisions were more complex, involving more side effects and substances. Remarkably, women took predominantly protease inhibitor-sparing regimens ($p = .05$).

Both genders reported only 15% of potential ART-related laboratory abnormalities but more than 50% had laboratory abnormalities. Notably, women had fewer elevated renal parameters ($p < .01$).

Conclusions: Men may attribute symptoms more often to HIV and maintain a treatment-regimen despite side effects, whereas women may be more prudent in

avoiding treatment side effects. Lacking awareness of laboratory abnormalities in both genders potentially indicates gaps in physician-patient communication. Gender differences in causal attributions of symptoms/side effects may influence treatment decisions.

Key words: HIV, antiretroviral treatment, gender, causal attribution, symptoms, side effects

INTRODUCTION

People with HIV with the option to take antiretroviral treatment (ART) now have the prospect of a near-normal life expectancy [1]. But despite access to ART, there is still excess mortality in people with HIV, which appears to be partially due to delaying, discontinuing, or not adhering to ART [2-4]. Patients' decisions about ART are strongly driven by weighing the risks of ART-related side effects against the benefits of preventing HIV-induced symptoms [5]. According to the Transtheoretical Model [6], the readiness to take and adhere to a treatment moves through five stages, precontemplation, contemplation, preparation, action and maintenance, and relapse. In the precontemplation stage, patients feel that ART is not appropriate for them at this certain point. In the contemplation stage, they weigh the benefits and risks of ART. In the preparation stage, patients have decided to start ART, in the action and maintenance stage they start taking ART and are committed to adhere to it, and in the relapse stage, patients start to reassess motivation and barriers to treatment. Thus, whether patients attribute their symptoms to HIV or ART may affect their readiness to adhere to ART. For example, individuals suffering from severe neuropathic pain and attributing this pain to HIV have a strong incentive to take ART, whereas attributing the same pain to ART may lead to the contrary. According to the Necessity Concerns Framework [7], attribution of symptoms to HIV may enhance perceived necessity to take and adhere to

ART, whereas attributions of symptoms to ART raises concerns about taking ART and is a predictor of intentional non-adherence.

The purpose of the present study was to examine causal symptom attributions among women and men with HIV, either to HIV or to ART, and to analyze a potential impact on their treatment decisions.

Although the distinction between patients' attributions of symptoms to HIV or ART may be a determinant of treatment motivation and success, symptom-checklists commonly combine HIV-related and ART-related symptoms in one category [8]. To our knowledge, there are few studies in predominantly male populations examining causal attributions of symptoms. The study of Johnson et al. [9] (88% men) demonstrated that patients taking ART made a distinction between HIV-related and ART-related symptoms. However, this study did not examine if this distinction had any impact on treatment decisions. Several qualitative studies describe that most people with HIV suffering from fatigue attribute this symptom at least in part to the virus [10-12]. Again, those studies included mostly men, and one study [10] included only people over age 50.

Furthermore, there may be differences between men and women in the causal attribution of symptoms that affect treatment decisions. A study on sex/gender differences found that women reported having more neuropathic symptoms, and consequently reducing and discontinuing DDI – a substance with the potential of inducing neuropathic symptoms – more frequently than men [13]. Several studies indicated sex-related differences in side effects of ART, encompassing symptoms such as lipodystrophy, neuropathy, and skin rashes, as well as laboratory abnormalities of liver enzymes, lipid profiles, insulin resistance, and lactic acidosis [14-17]. Surprisingly, none of those studies examined gender differences in the patients' causal attributions of those symptoms. Understanding causal attributions of symptoms of people with HIV and their gender differences may have important implications for HIV-treatment and management of side effects of ART.

Our present study bridges this gap in understanding by addressing three topics among women and men with HIV (including sex/gender differences) that may be of key relevance in clinical practice: (1) the prevalence and severity of symptoms and their attribution to HIV, ART or other causes, (2) the discontinuation of ART due to side effects, and (3) the presence and patient awareness of laboratory abnormalities potentially related to ART.

METHODS

DESIGN AND SAMPLE

This cross-sectional multicenter study was conducted between July 2004 and November 2006. Inclusion criteria for participation were being adult and diagnosed with HIV infection. People who did not take any antiretrovirals over the past six months were excluded from the study. The questionnaires were available in German, English, and French. However, all but one of

the 168 HIV-positive adults were fluent in German; only one woman filled out the English version. The group *All Around Women Special* conducted this nationwide study in collaboration with the *German Competence Network HIV/AIDS*. Patients were recruited at three University clinics (in Düsseldorf, Bochum, and Freiburg) and three private ambulatories with HIV-specialization (in Hamburg, Stuttgart, and Wiesbaden). We over-sampled women targeting a 1:1 sex ratio (46% female participants), which is why the centers mainly offered participation to all female patients and to a representative proportion of their male patients.

PROCEDURES AND MEASUREMENTS

The Institutional Review Boards of Bochum and Düsseldorf, Germany, approved the study. All participants gave written informed consent and completed a self-report questionnaire (age, sex, body weight, years since HIV-diagnosis and beginning of ART, ART over the past 6 months, and reasons for ART changes if applicable) and checklists of symptoms and ART-related laboratory abnormalities. In order to verify patient awareness of laboratory abnormalities, we collected the current laboratory reports from the treating physician on CD4+ -cells, viral load, hematology, and biochemistry.

The physical symptom checklist included 69 items (plus 11 women-specific items concerning menstrual and genital symptoms, and 3 men-specific items concerning genital symptoms), based on the checklist of the *AIDS Clinical Trials Group* [8], supplemented by items generated in co-operation with HIV-specialized physicians and people with HIV. On a scale from 0 (not at all) to 3 (very much), participants rated how bothersome symptoms were over the past 6 months. For each symptom scored above zero, a forced choice question asked for the participant's symptom attribution to HIV, ART, or other causes (if left blank, we rated the attribution as unclear). The self-report checklist of potentially ART-related laboratory abnormalities included renal and liver parameters, lipids, blood glucose, lactic acidosis, anemia among others. Physicians were blinded to the participants' responses. The full questionnaire is available at <http://www.kompetenznetz-hiv.de/>.

STATISTICAL ANALYSIS

All data were entered and quality controlled into statistical software (SPSS[®] version 12.0, Chicago, Illinois, USA). Missing data (i.e., laboratory values, body weight) were excluded from further analysis. Descriptive statistics and Chi-square analysis (including Fischer's exact tests) were the primary statistical methods used. To examine sex/gender differences for variables on ordinal or interval level, we used Student's t-tests. To rule out that significant gender differences on attribution of symptoms are explained by other variables, univariate analyses of variance controlling for potentially confounding variables such as age, time since diagnosis, time since taking antiretrovirals, and body weight were performed.

RESULTS

Significant sex-differences (Table 1) included age, body weight, and some markers of HIV-disease. Women were significantly younger, had a lower body weight, and had started ART more recently (despite of an average time since diagnosis of ten years for both men and women). Furthermore, CD4+-cell percentage was higher among women, but there were no sex-differences on absolute CD4+-cell counts and viral load log. In addition, women were significantly less likely to take protease inhibitors. Notably, 91% of the women and 82% of the men had an undetectable viral load under ART (despite that 9% women and men reported treatment interruptions over the past 6 months).

SYMPTOMS AND PATIENT'S CAUSAL ATTRIBUTION OF SYMPTOMS TO HIV OR ART
GENERAL OVERVIEW

Women and men did not differ on overall symptoms (27.22 ± 14.16 vs. 29.42 ± 15.80 , $t = -0.86$, $p = .391$) perceived mean symptom severity (0.75 ± 0.48 vs. 0.78 ± 0.48 , $t = -1.59$, $p = .115$) and percentage of symptoms attributed to ART ($29\% \pm 25$ vs. $28\% \pm 23$, $T = 2.79$, $p = .780$). Both genders indicated a clear causal symptom attribution ($81\% \pm 34$ vs. $81\% \pm 30$, $t = 0.15$, $p = .346$). As Figure 1 indicates, symptom attribution to HIV was significantly less likely among women ($16\% \pm 20$ vs. $25\% \pm 23$, $t = -2.63$, $p = .010$), whereas women were more likely to attribute symptoms (particularly sex-specific symptoms) to reasons other than HIV/ART ($31\% \pm 43$ vs. $24\% \pm 41$, $t = 2.30$, $p = .023$). To rule out that the sex-gender differences depicted in Figure 1 are explained by other covariates, we ran a univariate analysis of variance, controlling for age and years on ART. Results remained significant; sex/gender explained 51% of the variance in symptom attribution to HIV ($p = .008$) and 37% of variance in attribution to reasons other than HIV/ART ($p = .021$).

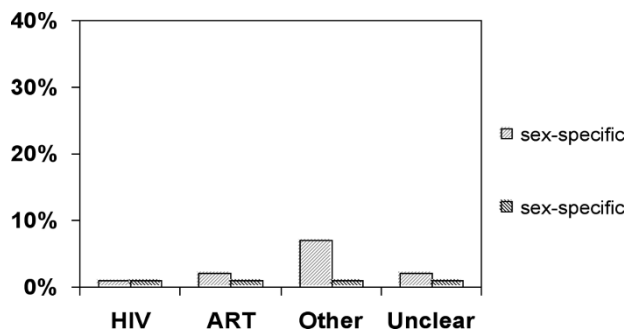


Fig. 1. Attribution of symptoms: Men were more likely to attribute their symptoms to HIV ($p < .01$). Women were more likely to attribute sex-specific symptoms (e.g., alterations in menstruation, impaired sexual function) to reasons other than HIV or antiretroviral therapy (ART) ($p < .001$).

Sex-specific symptoms were frequent in women (e.g., 50% reported painful menstruations, 42% vaginal discharge, 31% premenstrual syndrome, 27% heavy menstruations, 27% vaginal dryness, 21% pain during intercourse, 18% prolonged menstruations, 17% absent menstruations, and 13% weak menstruations), but only 15% of the women attributed their sex-specific symptoms to ART and 10% to HIV. Of the men, 32% reported erectile dysfunction and 20% ejaculation problems. In contrast, 46% of the men attributed their sex-specific problems to ART and 23% to HIV.

THE TOP 20 SYMPTOMS

Table 2 compares women and men on the 20 most common symptoms, their frequency, severity, and causal attribution. Among men, the two leading symptoms, fatigue and lack of energy (reported in over three-quarters of participants) as well as physical symptoms of lipodystrophy were significantly more likely attributed to HIV. In contrast, women were sig-

Table 1. Comparison of women (n = 78) and men (n = 90) on age, body weight, markers of HIV-disease, and antiretroviral treatment (ART).

| | Women M (SD) | Men M (SD) | Difference t |
|---------------------------|------------------|------------------|-----------------|
| Age | 42.71* ± 11.82 | 46.11* ± 9.28 | 2.08* |
| Body weight† | 65.07** ± 10.58 | 78.66** ± 19.45 | 3.61** |
| Years since HIV-diagnosis | 9.92 ± 5.55 | 10.51 ± 5.60 | 0.67 |
| Years since starting ART | 6.88* ± 4.45 | 8.38* ± 4.78 | 2.04* |
| CD4 cells/mm ³ | 505.58 ± 248.16 | 521.95 ± 299.18 | 0.38 |
| CD4 percentage | 29.37*** ± 10.07 | 22.06*** ± 10.47 | -4.40*** |
| Viral load log | 1.89 ± 0.74 | 2.08 ± 0.95 | 1.35 |
| | n (%) | n (%) | X ² |
| Undetectable viral load‡‡ | 62 (91%) | 65 (82%) | 2.46 |
| PI-sparing ART | 48 (62%) | 42 (47%) | 3.71* |

†Data on body weight was only available for 35 women and 33 men

‡‡Below 400 copies/ml

Significant difference between men and women at: * $p < .05$, ** $p < .01$, and *** $p < .001$

Table 2. Comparison of women (n = 78) and men (n = 90) on the 20 most common symptoms: Frequency of attribution to HIV and antiretroviral therapy (ART), total frequency and mean severity (scale from 0 - 3).

| Symptom | HIV (%) | | ART (%) | | Total (%) | | Severity M \pm SD | |
|---------------------------------------|---------|------|---------|-----|-----------|-----|---------------------|-----------------|
| | women | men | women | men | women | men | women | men |
| Fatigue | 19** | 40** | 24* | 11* | 82 | 78 | 1.69 \pm 1.05 | 1.50 \pm 0.99 |
| Lack of energy | 24* | 41* | 18 | 11 | 74 | 74 | 1.56 \pm 1.13 | 1.42 \pm 1.03 |
| Mood swings | 22 | 17 | 9 | 9 | 72 | 62 | 1.40 \pm 1.14 | 1.13 \pm 1.08 |
| Dry skin | 9 | 10 | 23 | 26 | 67 | 66 | 1.29 \pm 1.08 | 1.24 \pm 1.11 |
| Intestinal gas | 6 | 6 | 30 | 32 | 63 | 63 | 1.27 \pm 1.15 | 1.22 \pm 1.11 |
| Fat loss from limbs/ buttocks/face | 5* | 16* | 42 | 37 | 56 | 67 | 1.26 \pm 1.24 | 1.36 \pm 1.23 |
| Sleep disturbances | 10 | 14 | 19 | 14 | 63 | 60 | 1.17 \pm 1.16 | 1.20 \pm 1.12 |
| Depressed feelings | 22 | 17 | 10 | 11 | 63 | 59 | 1.23 \pm 1.16 | 1.07 \pm 1.10 |
| Loss of stamina | 26 | 30 | 9 | 11 | 60 | 61 | 1.18 \pm 1.16 | 1.20 \pm 1.12 |
| Lethargy | 18 | 27 | 14 | 11 | 59 | 60 | 1.15 \pm 1.15 | 1.11 \pm 1.08 |
| Pain/numbness in hands/feet | 12 | 19 | 19 | 19 | 56 | 61 | 1.17 \pm 1.18 | 1.17 \pm 1.09 |
| Prominent veins | 3* | 12* | 32 | 29 | 49 | 62 | 1.10 \pm 1.25 | 1.31 \pm 1.19 |
| Lack of interest in sex | 14 | 14 | 13 | 23 | 54 | 62 | 1.00 \pm 1.23 | 1.13 \pm 1.05 |
| Difficulties concentrating | 17 | 26 | 18* | 7* | 56 | 52 | 1.05 \pm 1.07 | 0.78 \pm 1.07 |
| Night sweats | 24 | 24 | 8 | 12 | 50 | 58 | 0.85 \pm 1.01 | 1.02 \pm 1.04 |
| Diarrhea | 8 | 14 | 25 | 28 | 47 | 57 | 0.82 \pm 1.00 | 1.09 \pm 1.09 |
| Headache | 10 | 8 | 8 | 24 | 50 | 56 | 0.91 \pm 1.07 | 0.89 \pm 0.98 |
| Skin itching | 9 | 11 | 18 | 23 | 47 | 57 | 0.81 \pm 0.98 | 0.94 \pm 1.01 |
| Fat gain in abdomen | 1 | 7 | 32 | 26 | 51 | 56 | 1.03 \pm 1.14 | 0.84 \pm 1.07 |
| Muscle aches | 6 | 9 | 21 | 14 | 45 | 50 | 0.92 \pm 1.16 | 0.79 \pm 0.93 |

Chi square test indicates significant difference between men and women at:

* $p < .05$ and ** $p < .01$

nificantly more likely to interpret fatigue and difficulties concentrating as ART-related. Even after control for age and duration of ART, sex/gender differences on symptom attribution remained significant for fatigue ($R^2 = 0.88$, $p = .003$) and lack of energy ($R^2 = 0.37$, $p = .048$), but not for difficulties concentrating and signs of lipodystrophy. Thus, the finding that men are more likely than women to attribute fatigue and lack of energy to HIV is not due to differences in age or duration of ART. However, sex/gender differences in attribution of lipodystrophy and difficulties may be explained by confounding variables.

MOST COMMON SYMPTOMS RELATED TO HIV AND ART

Ranking of the top five symptoms related to HIV and ART were similar in women and men (see Table 2). Loss of stamina and lack of energy were among the top five symptoms attributed to HIV for both genders. For women, night sweats, mood swings and depression, and for men fatigue, lethargy, and difficulties in concentrating further ranked among the top five HIV-symptoms. Both genders interpreted lipodystrophy (i.e., fat loss from limbs, buttocks, or face, prominent

veins, and fat gain on the abdomen) and gastrointestinal symptoms (i.e., intestinal gas and diarrhea) as the top side effects of ART. The leading two sex-specific symptoms attributed to HIV were heavy menstruations (5%) and vaginal dryness (5%) for women, and erectile dysfunction (8%) and ejaculation problems (5%) for men. The main two sex-specific symptoms interpreted as side effects of ART were heavy (8%) or absent menstruations (8%) for women, and again erectile dysfunction (14%) and ejaculation problems (10%) for men.

DISCONTINUATION OF ART DUE TO SIDE EFFECTS

Discontinuation such as switches and interruptions of ART due to side effects were common among both genders (see Table 3). The influence of side effects on decisions about ART was more complex among women, involving more antiretroviral substances and more side effects. For example, women discontinued lamivudine and lopinavir boosted with ritonavir (LPVr) significantly more often in order to avoid lipodystrophy, metabolic changes (i.e., elevated lipids or blood glucose), and gastrointestinal problems. Thus, women were taking LPVr significantly less often

Table 3. Comparison of women (n = 78) and men (n = 90) on discontinuations of antiretrovirals due to side effects over the past 6 months.

| | Women(%) | Men(%) | |
|------------------------------|----------|--------|--|
| <i>Discontinuations</i> | 19 | 18 | |
| Switch | 10 | 9 | |
| Pause | 9 | 9 | |
| <i>Antiretrovirals</i> | | | |
| Lamivudine | 12* | 2* | |
| Stavudine | 6 | 3 | |
| Lopinavir + Ritonavir boost | 5* | 0* | |
| Zidovudine | 4 | 2 | |
| Tenofovir | 4 | 1 | † Other antiretrovirals included single cases of Nevirapine and Emtricitabine in women and men, and Didanosine, Tripanavir + Ritonavir boost, and Fuzeon in men. |
| Abacavir | 4 | 1 | |
| Atazanavir + Ritonavir boost | 3 | 0 | |
| Other antiretrovirals† | 3 | 6 | ‡ Other side effects included single cases of amenorrhea, teratotoxic potential, adherence barrier during vacation, changes in taste, and resistance mutations in women, and kidney stones, pain at injection site, nightmares, and depression in men. |
| <i>Side effects</i> | | | |
| Lipodystrophy | 8 | 2 | |
| Metabolic changes | 4 | 3 | |
| Polyneuropathy | 1 | 3 | |
| Gastrointestinal problems | 4 | 7 | Chi square test indicates significant difference between men and women at: |
| Skin problems | 3 | 1 | |
| Other side effects‡ | 6 | 4 | * p < .05 |

Table 4. Comparison of women (n = 77) and men (n = 85) on frequency of laboratory abnormalities: laboratory reports, self-reports, and patient awareness.

| Laboratory abnormality | Laboratory report | | Self-report | Awareness† | Men | | Women | |
|------------------------|-------------------|---------|-------------|------------|-----------|---------|-----------|---------|
| | Women (%) | Men (%) | | | Women (%) | Men (%) | Women (%) | Men (%) |
| Anemia | | | | | | | | |
| Grade 1 | 18 | 12 | 1 | 0 | 7 | 0 | | |
| Renal parameter‡ | | | | | | | | |
| Grade 1 | 7** | 25** | 0 | 0 | 0 | 0 | | |
| Liver parameter‡‡ | | | | | | | | |
| Grade 1 | 55 | 68 | 21 | 16 | 38 | 23 | | |
| Grade 2 | 42 | 54 | 13 | 10 | 31 | 18 | | |
| Grade 3 | 9 | 11 | 5 | 4 | 56 | 36 | | |
| Hyperglycemia | | | | | | | | |
| Grade 1 | 4 | 4 | 3 | 2 | 75 | 50 | | |
| Grade 2 | 12 | 14 | 0 | 1 | 0 | 8 | | |
| Grade 3 | 8 | 10 | 0 | 0 | 0 | 0 | | |
| Elevated Lipids‡‡‡ | | | | | | | | |
| Grade 1 | 3 | 0 | 0 | 0 | 0 | 0 | | |
| Grade 2 | 1 | 4 | 0 | 1 | 0 | 50 | | |
| Grade 3 | 55 | 66 | 11 | 15 | 20 | 23 | | |
| Elevated Lipids‡‡‡ | | | | | | | | |
| Grade 1 | 47 | 54 | 8 | 10 | 17 | 18 | | |
| Grade 2 | 8 | 10 | 3 | 5 | 38 | 50 | | |
| Grade 3 | - | 2 | - | 1 | - | 50 | | |
| Lactic Acidosis‡‡‡‡ | | | | | | | | |
| Grade 1 | 8 | 19 | 0 | 0 | 0 | 0 | | |

† Awareness refers to the percentage of laboratory abnormalities that were patient-reported
 ‡ Abnormality in at least one renal parameter (creatinine, urea, uric acid, electrolytes)
 ‡‡ Abnormality in at least one liver parameter (ALT, AST, ALP, GGT, bilirubin –except for benign hyperbilirubinemia under Atazanavir or Indinavir)
 ‡‡‡ Abnormality in at least one lipid parameter (triglycerides, LDH, HDLH, total cholesterol)
 ‡‡‡‡ Physician reports are only available on 13 women and 21 men.
 Chi square test indicates significant difference between men and women at:
 * p < .05 and **p < .01

(10% vs. 30%, $p < .01$). Taking LPVr was significantly associated with elevated lipid profiles in the laboratory reports. The mean grade of lipid abnormalities was higher in patients taking LPVr vs. those not taking LPVr (0.97 ± 0.67 vs. 0.66 ± 0.66 , $p = .02$).

PATIENT AWARENESS OF LABORATORY ABNORMALITIES

Overall, both genders did not differ on awareness of laboratory abnormalities, reporting only 15% of potentially ART-related laboratory abnormalities, such as anemia, elevated renal or liver parameters, lipids, or glucose (see Table 4). Liver parameters and lipids were elevated in more than half of the patients. However, laboratory abnormalities were mostly mild (grade 1 according to the toxicity grading scale [18]). Fewer than one-third of the moderate (grade 2) laboratory abnormalities, and fewer than half of the severe (grade 3) laboratory abnormalities were reported by the patients as potential side effects of ART. There were no significant sex differences on laboratory abnormalities except for renal parameters, which were significantly less likely to be elevated among women.

DISCUSSION

The purpose of this study was to examine symptoms and symptom attribution to HIV or ART, discontinuation of ART due to side effects, and awareness of potentially ART-related laboratory abnormalities among people with HIV; while considering sex/gender differences. Participants were recruited from HIV clinics and private ambulatories, and thus more representative of the "real world" compared to those selected for clinical trials. We identified the main symptoms of which people with HIV suffered from, and whether they blamed HIV, ART, or other causes for these symptoms. Interestingly, women and men also differed in their treatment decision-making in order to avoid side effects of ART. Finally, this study revealed striking gaps in patient awareness of laboratory abnormalities, potentially modifiable via physician-patient communication.

WHAT DO PEOPLE WITH HIV SUFFER FROM THE MOST?

Both genders reported a wide range of symptoms related to the general energy level (fatigue, sleep, and loss of energy), psychological well-being (depression, mood swings, lack of libido), physical and metabolic changes (lipodystrophy syndrome), and gastrointestinal, dermatological, and neurological problems. The high prevalence of mild to moderate symptoms is consistent with findings of other studies [9, 19-23]. What distinguishes our study is that we added symptoms relevant from the perspective of people with HIV to our symptom checklist. Thus, an average number of 27-29 symptoms was established, which is much higher than numbers reported in other studies using a brief instrument [21, 23]. Furthermore, we found a relatively high prevalence of sex-specific symptoms related to sexual function (up to 32%) and menstruation (up to 50%).

WHAT IS BLAMED, THE DRUGS OR THE DISEASE?

Participants attributed a higher percentage of their symptoms to ART than to HIV. In our study, the prevalence of side effects [9, 21-23] and symptoms of HIV [9, 24] was comparable to other studies. Consistent with Johnson (2003), lipodystrophy and gastrointestinal problems were most commonly interpreted as side effects of ART, whereas the low energy levels and night sweats were mostly attributed to HIV.

An important finding, also supported by Johnson (2003), is that most participants were able to clearly identify the cause of their symptoms. However, in the Johnson sample, the attribution of symptoms to HIV/ART was higher than in our sample, but Johnson (2003) used an HIV-specific symptom checklist, which might explain this difference. The findings of the Women's Interagency HIV Study corroborate the high prevalence of symptoms attributed to other causes in women with HIV [20].

HIV OR ART — DO WOMEN AND MEN DIFFER IN THEIR CAUSAL ATTRIBUTIONS?

The most striking finding of our study was the gender difference in causal attributions. Men were more likely to relate their symptoms to HIV, which may encourage them to take ART, whereas women were more likely to attribute fatigue to ART. Both can be debilitating symptoms that may discourage them to take the medication.

Although women attributed sex-specific symptoms mostly to causes not related to HIV and its treatment, the significant proportion of menstruation alterations related to ART deserves acknowledgement in clinical practice. Again, the Women's Interagency Study found that HIV-positive women are at increased risk for some menstrual changes, although the absolute frequency of most abnormalities is low [25].

Furthermore, the high prevalence of problems affecting sexual intercourse that men attributed to ART (lack of interest in sex, erectile dysfunction, and ejaculation problems) should be recognized in clinical practice since this might have impact on the readiness to take ART. In addition, men may be encouraged to take self-medications to enhance their sexual functioning, which could potentially interfere with ART [26].

SWITCHING ART WHEN IT IS SMART —DO WOMEN AND MEN DIFFER?

Although both genders commonly experienced side effects of ART that had an impact on their treatment decisions, four findings of our study may indicate gender differences in switching ART in order to avoid side effects. First, a more complex spectrum of treatment changes among women, driven by more symptoms/side effects attributed to ART. Second, less intake of protease inhibitors among women, potentially mitigating or reversing treatment-associated lipodystrophy and metabolic complications by omitting these components of ART [27]. Third, the disproportionate prevalence of renal dysfunction among men, possibly reflecting a higher exposure to toxicities of ART [28]

(in our study, men were taking ART on average 18 months longer than women). Finally, since in the German population women are known to report a higher frequency and severity of symptoms [29], we expected to have similar findings in the population of people with HIV. However, in our study women and men with HIV did not differ on the frequency and severity of symptoms, which also may indicate that women were more successful in reducing side effects of ART.

SHARING LAB RESULTS – GAPS IN PHYSICIAN-PATIENT COMMUNICATION?

Another imperative discovery of our study was the incongruence between physicians' and patients' reports of laboratory abnormalities. Only one of seven participants indicated potentially ART-related laboratory abnormalities that were documented in the physician's records. This might partially be explained by attribution of laboratory abnormalities to other causes, such as co-infection with viral hepatitis. Some laboratory abnormalities may simply be not avoidable, such as lipid and glucose elevations in patients with a predisposition to develop a metabolic syndrome, or elevated liver enzymes in patients with a hepatitis co-infection. Clinical significance of laboratory abnormalities depends on the treatment, the treatment experience, and the patient's vulnerability to develop certain side effects. Since the majority of the laboratory abnormalities were mild, physicians may not have discussed them with their patients or patients did not recall the discussion. A patient's forgetfulness of laboratory abnormalities may indicate that his/her focus is on benefit rather than on risk of the treatment, weighing long survival with HIV against laboratory alterations such as elevated lipids, liver enzymes, or lactic acidosis. By focusing on HIV, some patients may ignore their individual risk of cardiovascular or liver disease. Thus, a patient's "selective memory" may serve as an individual strategy to cope with the disease and its treatment and to avoid panic about minor laboratory alterations.

Nevertheless, in the context of ART, abnormalities of liver enzymes, even if they are mild, require further examination of the etiology and may be an indicator of ART-related mitochondrial injury and hepatic steatosis [30, 31]. Since potentially ART-related laboratory abnormalities might be amenable to change by treatment modifications, the lack of patients' awareness of these abnormalities should be addressed. Keeping the lines of communication open and transferring knowledge about serious side effects is an essential element in patient-physician relationship.

LIMITATIONS

A limitation of this study is that the questionnaires were self-administered and the data is thus prone to self-report and recall bias. Furthermore, symptoms that were being treated so that they were not bothersome during the study visit (e.g., pain controlled with analgesics) may not have been reported. Also, it is difficult to compare the results of this study to other research, since different methods of assessing symptoms yield large differences in the reported prevalence.

For example, the percentage of patients reporting symptoms on a checklist is higher compared to physicians' questioning [32], and the longer the symptom checklist, the more symptoms that are potentially reported. In addition, study design issues may limit the generalizability of our findings, since we did not include a control group, so that there is no internal comparison to people with HIV who are not taking ART or to the general population. In addition we did not control for other potential confounders such as race/ethnicity, socioeconomic status, sexual orientations, and substance use. Finally, women and men were not matched for length of exposure to ART, with women having on average 18 months less ART-exposure than men, which may account for some variance in symptoms and laboratory abnormalities.

Conclusions

Men and women with HIV suffer from a wide range of symptoms but attribute these symptoms more to side effects of the treatment than to effects of the disease. This is more true for women than for men, since the likelihood of symptom attribution to HIV is greater among men, which may motivate men to take ART despite side effects. Women, on the other hand, view their symptoms more likely as side effects of ART and are more prepared to switch or interrupt treatment in order to avoid toxicity. Furthermore, patients' causal attributions of sexual or menstrual dysfunction are relevant for clinical practice. Finally, tackling potentially ART-related laboratory abnormalities even in their early stages and adjusting treatment accordingly might help reducing toxic effects of ART.

In summary, as patients' causal attributions of symptoms to HIV or ART have an influence on treatment decisions, their perspectives are of clinical importance. Clinicians need to be aware of gender differences in causal attributions of symptoms and communicate about the patients' perceptions of the causes of their symptoms, as well as potentially ART-related laboratory abnormalities.

Acknowledgements: The authors thank the Federal Ministry of Education and Research for funding this study within the frame of the German Competence Network HIV/AIDS and all participants for volunteering to complete the questionnaires.

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Received: October 22, 2008 / Accepted: March 4, 2009

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