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Sex Differences in Antiretroviral Therapy-Associated Intolerance and Adverse Events

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Abstract

Although women account for a substantial proportion of the global population infected with HIV, most clinical trials evaluating the safety and efficacy of specific antiretroviral therapy regimens have been preformed in predominantly male cohorts. Our knowledge of the sex differences associated with responses to these treatments is therefore limited. Potentially sex-specific influences, such as endogenous or exogenous hormones, could impact antiretroviral tolerance. Women also have different pharmacokinetic profiles for selected antiretrovirals compared with men. These factors could influence how women respond and react to antiretrovirals. Several observational studies have described a higher frequency of antiretroviral-related adverse effects among women compared with men. Women appear to be at an especially high risk for lactic acidosis, nevirapine-associated rashes and hepatotoxicity, and fat redistribution after highly active antiretroviral therapy exposure. Although a statistical association between antiretroviral toxicity and pregnancy has not been described, pregnancy may provide an additional influence on the toxicity of several antiretrovirals or antiretroviral combinations. Potential tolerability should be an important component in discussions of antiretroviral options among women.

Today women account for nearly half of the global HIV-infected population, estimated to be nearly 40 million individuals.[1] Although a substantial proportion of persons with HIV or AIDS are women, our knowledge about antiretroviral pharmacokinetics, efficacy and safety comes from clinical trials, which have predominantly enrolled men.[2] Although it is probably reasonable to generalise results, women do differ in several respects compared with men. Because of these differences, antiretroviral-related toxicities and the subsequent overall effectiveness of specific antiretroviral therapies may not be the same in men and women.

This article reviews what is known about sex differences in regards to antiretroviral-related adverse events and intolerance. To ensure a comprehensive review, a MEDLINE search for English language articles from 2003 to July 2004 was performed. The heading of antiretroviral agents was 'exploded' using subheadings of 'poisoning' and 'adverse effects'.

1. Unique Sex Influences on Antiretroviral Pharmacokinetics

Antiretroviral pharmacokinetic profiles may be modestly influenced by sex or other sex-specific

factors, such as pregnancy or hormonal therapies.[3-17] Differences in hepatic enzyme expression may account for the sex-associated pharmacokinetic variability.[18] The predominant hepatic enzymes that metabolise many antiretrovirals are the cytochrome P450 (CYP) 3A subfamily. These have been shown to differ by sex in both humans and animals,[18] and can be influenced by endogenous and exogenous hormones.[19]

Higher antiretroviral concentrations could potentially be associated with a higher risk for intolerance or adverse events. Lower concentrations may be less efficacious and allow the emergence of antiretroviral resistance. Specific pharmacokinetic differences between the sexes are shown in table I. As illustrated in the table, women appear to have higher concentrations or decreased clearance of several antiretroviral agents.[3-11] As described later, antiretrovirals with potentially higher serum concentrations in women may be associated with higher frequencies of adverse effects in this population. However, higher serum antiretroviral concentrations may also potentially improve efficacy. In a pharmacokinetic study of saquinavir, females had both higher area under the concentration-time curve (AUC) values for saquinavir and a greater probability for having non-detectable HIV RNA levels compared with men.[20]

Table I. The influence of sex on selected antiretroviral pharmacokinetic parameters in non-pregnant adults (reproduced from Clark and Squires,[12] with permission from Future Drugs Ltd)

Drug	Sex difference (women compared with men)	Reference
Amprenavir	No difference	3
Atazanavir	Mean concentrations were 20% higher in women	4
Indinavir	C_{min} was 22% less in women	3
Lopinavir	Mean concentrations were 20% higher in women	4
Nelfinavir	No difference	5
Saquinavir	Higher concentrations and decreased clearance in women[a]	6
Efavirenz	Increased concentrations in women	7
	No difference in concentrations	8
	Decreased concentrations in women	5
	No difference in clearance	8,9
Nevirapine	Higher concentrations in women	10
	Decreased clearance in women[b]	11

a The clearance of saquinavir was 46.7% of the clearance in males, which increased the AUC by approximately 50% and prolonged the half-life to 6.1 hours.

b The clearance for women was 3.02 L/hour for women compared with 3.97 L/hour for men.

AUC = area under the concentration-time curve; C_{min} = minimum concentration.

Women may be at risk for suboptimal drug concentrations during pregnancy. Limited data from small studies have shown that pregnant women have lower or more variable concentrations of saquinavir, nelfinavir, indinavir or lopinavir/ritonavir than non-pregnant women.[4,13-17] Flexner[4] suggested that possible explanations for this could include induction of hepatic drug-metabolising enzymes, changes in gastrointestinal transit times, increases in body water and fat, and changes in the expression of drug transporters.

The effect of endogenous or exogenous hormones on antiretroviral pharmacokinetic profiles is largely unknown, but is another possible sex-specific influence. One study has shown that zidovudine pharmacokinetic parameters remain unchanged during the three phases of the menstrual cycle.[21] Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates of CYP3A4.[22] Some PIs (e.g. amprenavir and ritonavir) are also inducers of certain CYP enzymes and NNRTIs can act as inducers (nevirapine) or inhibitors (delavirdine) of these enzymes, or be a mixed inducer and inhibitor (efavirenz).[22] Ethinylestradiol, a component in oral contraceptive therapies, is also metabolised hepatically through the CYP system.[23] Not surprisingly, PIs and NNRTIs often have significant interactions with oral contraceptive therapies. Most pharmacokinetic studies have concentrated on the effects of antiretrovirals on ethinylestradiol and norethisterone, as shown in table II.[22] Pharmacokinetic data on the effect of hormonal therapies on antiretroviral concentrations only exists for two PIs. Concurrent use of amprenavir (or fosamprenavir) and oral contraceptives is not recommended because of the effect of the oral contraceptive on the pharmacokinetics of amprenavir or fosamprenavir (the concentrations are lowered).[22] Oral contraceptives do not

Table II. Pharmacokinetic interactions between protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapies and oral contraceptive pills[22]

Drug	Concentration of ethinylestradiol (EE) or norethisterone (NE)
Indinavir	Increases EE 24% Increases NE 26%
Atazanavir[a]	Increases EE AUC 48% Increases NE AUC 110%
Efavirenz[a]	Increases EE 37%
Ritonavir[a]	Decreases EE 40%
Nelfinavir[a]	Decreases EE 47% Decreases NE 18%
Amprenavir[b]	Decreases amprenavir levels 20%
Lopinavir[a]	Decreases EE 42%
Nevirapine[a]	Decreases EE 20%

a Additional or alternative contraceptive methods are recommended.

b Concurrent use of amprenavir (or fosamprenavir) with oral contraceptive pills is not recommended.

AUC = area under the concentration-time curve.

affect saquinavir pharmacokinetics,[24] the only other PI for which there is published information.

Nucleoside reverse transcriptase inhibitors (NRTIs) are considered to be prodrugs, since their active moiety is the triphosphate anabolite that is formed intracellularly.[25] Information on intracellular NRTI triphosphates is critical for the understanding of NRTI pharmacokinetics, but data is limited because of the difficult procedures needed to measure NRTI anabolites.[26] One study that evaluated sex differences in zidovudine and lamivudine triphosphate concentrations in patients receiving these drugs found higher concentrations of NRTI anabolites in women than men (2.3- and 1.6-fold for zidovudine and lamivudine, respectively).[27] Women also reached an HIV-RNA level of <50 copies/mL twice as fast as did men.[27]

2. Sex Differences in Antiretroviral-Associated Adverse Events

Several studies have suggested that sex can influence the frequency, presentation and severity of specific selected antiretroviral-related adverse events.[28-48] The vast majority of clinical trials have not been statistically powered to determine whether or not sex is associated with specific antiretroviral toxicities. Regardless, multiple studies have shown that women have an increased frequency and severity of specific adverse effects compared with men, as shown in table III and table IV.[28-48]

Although the mechanism for sex differences in antiretroviral-induced adverse reactions is unknown, it is possible that weight and pharmacokinetic differences may play a role, as suggested previously. For example, studies have shown women to have both higher concentrations and lower clearance rates of nevirapine than men[11,12] and this is one drug that clearly has a sex differential in its adverse effect profile.[29-37] However, although patients with elevated liver function tests have been shown to have higher trough concentrations of unbound nevirapine than persons with normal liver function tests, no strong association between hepatotoxicity and total nevirapine concentrations has been demonstrated.[49]

In addition to a direct influence of sex on the risk of antiretroviral adverse events, sex-immunological interactions may also play a role. For example, a higher baseline CD4+ cell count appears to be an important influence on the risk for developing nevirapine toxicity, particularly among women. Experts recommend sex-specific CD4+ cell count thresholds for initiating nevirapine (<250/mm^3 in women vs 400/mm^3 in men).[22]

Table V shows all currently available antiretroviral agents, stratified by class.[50] The NRTIs have been associated with various adverse effects such as myelosuppression, pancreatitis, gastrointestinal intolerance, peripheral neuropathy, myopathy and lactic acidosis.[22] Many of these adverse events are thought to be mediated through mitochondrial toxicity.[22]

As shown in the table III, women appear to have greater intolerance to NRTIs, particularly didanosine, than men. Interestingly, didanosine is different from many other drugs in that it requires a dosage adjustment according to bodyweight (stavudine also requires such an adjustment). Low-weight women may be especially vulnerable to the adverse effects of didanosine, potentially because of higher blood concentrations of this drug.

Table III. Studies demonstrating a sex difference in nucleoside reverse transcriptase inhibitors (NRTIs); or non-nucleoside reverse transcriptase-associated adverse reactions in non-pregnant adults (reproduced from Ofotokun and Pomeroy,[2] with permission from the International AIDS Society-USA)

Study	Regimen	Sex difference
Squires et al.,[28] START I and START II	NRTIs	Higher frequency of adverse events in women
Currier et al.,[29] ACTG 175	NRTIs	Higher likelihood of reducing dose or stopping didanosine-containing regimen in women
Moore et al.[30]	NRTIs	Nearly 3-fold increase in risk for adverse events because of didanosine
Boxwell and Styrt[31]	NRTIs	83% of lactic acidosis cases and 85% of fatal cases occurred in women
Mazhude et al.[32]	Nevirapine-containing	11.7-fold increase in risk of rash in women
Bersoff-Matcha et al.[33]	Nevirapine-containing	7-fold increase in risk of rash in women; women were 3–5 times more likely to discontinue nevirapine use
Wong et al.[34]	Nevirapine-containing	Higher rate of rash in women
Antinori et al.[35]	Nevirapine-containing	Higher rate of rash in women
Bartlett[36]	Nevirapine- or efavirenz-containing	2-fold higher incidence of severe LFT elevations among women receiving nevirapine
Sanne[37]	Nevirapine- or efavirenz-containing	Higher frequency of hepatotoxicity among women

ACTG = AIDS Clinical Trials Group; **LFT** = liver function test; **START** = sex differences in the Selection of Thymidine Analog Regimen Therapy trials.

Although the studies showing a higher frequency of didanosine-related adverse effects in women than men were performed prior to the availability of the newer enteric-coated formulation of didanosine, the incidence of pancreatitis and other systemic adverse effects would not be anticipated to change. However, the enteric-coated didanosine does ameliorate the gastrointestinal adverse effects caused by the buffer in the old formulation of didanosine. As previously described,[27] the relatively higher concentrations of intracellular triphosphates (as a result of the phosphorylation of NRTIs to their active anabolites) among women than men likely contribute to the higher risk for NRTI-associated adverse events.

The combination of didanosine and stavudine has been noted to be associated with a relatively high risk for toxicities, particularly of peripheral neuropathy, pancreatitis and lactic acidosis. This combination has also been linked to deaths among pregnant women due to severe lactic acidosis. The guidelines recommend that this combination be avoided unless other options have been exhausted.[22]

Tenofovir, the one currently available nucleotide reverse transcriptase inhibitor (RTI), has been associated with renal dysfunction.[22] In addition to prior renal toxicity with adefovir or cidofovir, low weight and female sex may also play a role in increasing the risk for this complication.[51,52]

Lactic acidosis is an uncommon but serious antiretroviral-related adverse event thought to be related to the use of NRTIs.[22] A large review of published cases of antiretroviral-associated lactic acidosis (n = 56) found that women had a relative risk of 2.5 for this complication compared with men.[53] The US FDA report supports this finding. In a review of 60 cases of lactic acidosis, 83% occurred among women receiving a RTI and 85% of the 20 fatal cases were in women. Hepatic steatosis occurred in 71% of the women and pancreatitis occurred in 29%.[31]

Pregnancy is a potential confounder when evaluating the association between sex and specific antiretroviral-related adverse events such as lactic acidosis. Pregnant women taking selected antiretrovirals appear to be at particularly high risk for this complication. As previously mentioned, maternal deaths (and some associated fetal deaths) due to lactic acidosis have been reported in pregnant or post-partum women who were receiving stavudine and didanosine along with other drugs before pregnancy.[22] The syndrome of lactic acidosis and hepatic steatosis is similar to the acute fatty liver of

pregnancy that occurs more frequently among women with heterozygous defects of mitochondrial fatty-acid metabolism who are carrying fetuses that are homozygous for the same defect.[54] Clinicians should have a low threshold of suspicion for lactic acidosis among any pregnant women receiving NRTIs who have persistent abdominal complaints, particularly if they have accompanying hepatitis or pancreatitis.

Common adverse effects due to NNRTIs are rash and hepatitis.[22] Efavirenz is also associated with CNS adverse effects.[22] As shown in table III, nevirapine-associated toxicities (rash and hepatitis) are more frequent among women than men.[32-37] As previously stated, the immunological status of the patient appears to interact with sex and is also an important influence on the responses to antiretroviral therapy. Nevirapine initiation in women with a CD4+ cell count >250/mm^3 is contraindicated because this population is at highest risk for severe adverse effects.[19] Efavirenz-associated CNS toxicities do not appear to differ by sex. These observations are consistent with pharmacokinetic data, if the hypothesised relationship between drug concentrations and risk for adverse effects is valid. Although nevirapine concentrations are consistently higher among women than men,[10,11] studies of efavirenz have shown varying pharmacokinetic profile results, demonstrating both lower and higher concentrations in sex comparisons.[5,7-9]

As previously stated, pregnancy may influence the risk for selected complications.[22,55,56] A statistically significant association between pregnancy and nevirapine-related hepatotoxicity has not been described, but recent studies of pregnant HIV-infected women have demonstrated that this population can experience life-threatening hepatic complications due to nevirapine.[55,56] At the 2004 Conference on Retroviruses and Opportunistic Infections, the results from a prospective, randomised, open-label study comparing nelfinavir/zidovudine/lamivudine with nevirapine/zidovudine/lamivudine among pregnant women were reported. This study was prematurely stopped because of higher than expected

Table IV. Studies demonstrating a sex difference in metabolic complications in non-pregnant adults taking highly active antiretroviral therapy (HAART) [reproduced from Clark and Squires,[12] with permission from Future Drugs Ltd]

Study	No. of patients	Sex difference
Nguyen et al.[38]	222	Women were more likely to have lipodystrophy (10.8% women vs 2% men, p < 0.01) and neurological complications (12.6% women vs 8% men, p < 0.01) than men
Jacobson et al.[39]	371	Men were more likely to have fat atrophy than women
Koko-Ekong et al.[40]	87	Men were more likely to have fat atrophy than women, but women were more likely to experience fat gain, particularly buffalo humps and increases in abdominal girth
McDermott et al.[41]	265	Appendicular fat mass was associated with HAART in men, but not in women. Bone mineral content loss was associated with HAART in men but not in women
Galli et al.[42]	2258	Morphological changes were more common among women than men
Thiebaut et al.[43]	156	Fat wasting occurred less often in women than men (women 10% vs men 17%), but fat accumulations were similar
Falutz et al.[44]	336	In adjusted analysis, women were more likely than men to be diagnosed with increased regional body fat (p = 0.03)
Lichtenstein et al.[45]	143	Female sex associated with fat accumulation (p = 0.0003)
Martinez et al.[46]	494	Lipodystrophy with central obesity was more frequent among women than men (p = 0.0058)
Clark et al.[47]	222	Triglyceride level increases associated with PI therapy were significantly greater in men than women (men 15.4% vs women 4.6%, p = 0.033)
Pernerstorfer-Schoen et al.[48]	27	Increased levels of triglycerides, leptin, LDL and total cholesterol were more distinct in women than men. Fasting insulin levels and the LDL/HDL ratio only increased in women (women vs men, p = 0.02)

HDL = high-density lipoprotein; **LDL** = low-density lipoprotein; **PI** = protease inhibitor.

Table V. Currently available antiretroviral drugs (reproduced from Besch,[50] with permission)

Class	Drugs
NRTIs	Zidovudine, didanosine, zalcitabine, stavudine, abacavir, lamivudine, emtricitabine
Nucleotide RTIs	Tenofovir
NNRTIs	Nevirapine, delavirdine, efavirenz
PIs	Saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir
Fusion inhibitors	Enfuvirtide

NNRTIs = non-nucleoside reverse transcriptase inhibitors; **NRTIs** = nucleoside reverse transcriptase inhibitors; **PIs** = protease inhibitors; **RTIs** = reverse transcriptase inhibitors.

nevirapine toxicity. Five of 17 women receiving nevirapine had adverse events that led to treatment discontinuation and one of the five women experienced fulminate hepatic failure and death.[55] Information from the FDA that was presented at the same meeting also described the relatively high frequency of nevirapine- or didanosine/stavudine-related hepatotoxicity among pregnant women. Hepatic failure was reported with the use of nevirapine (n = 6), zidovudine (n = 4), didanosine (n = 4) and stavudine (n = 4). Five women died because of hepatic failure during pregnancy or the post-partum period. Of these five, three were receiving zidovudine/lamivudine/nevirapine, two were receiving didanosine/stavudine/nevirapine and one received didanosine/stavudine/nelfinavir. Deaths among women receiving zidovudine/lamivudine/nevirapine were due to hepatic necrosis, while the deaths in subjects receiving didanosine/stavudine were associated with lactic acidosis.[56]

A variety of adverse effects are associated with PIs, but gastrointestinal intolerance is probably the most frequent and is seen with nearly all PIs.[22] Two studies evaluating ritonavir, probably one of the most difficult PIs to tolerate, found women had a higher frequency of adverse effects, primarily gastrointestinal toxicities, compared with men.[57,58] Among patients taking nelfinavir, women experienced more abdominal pain and itching (although these were infrequent adverse effects), but men experienced more diarrhoea.[59]

Potential metabolic complications of antiretroviral therapy include insulin resistance and glucose intolerance, dyslipidaemia, changes in body fat distribution and bone disorders.[22] Although most PI therapies have particularly been linked to glucose and lipid abnormalities,[22] the mechanisms underlying metabolic complications and their relationship to specific antiretroviral therapies is not clearly delineated.

Studies performing sex comparisons for selected metabolic complications among non-pregnant adults are shown in table IV. Most of the information pertains to fat redistribution differences. Information on sex differences in glucose and lipid sequelae from highly-active antiretroviral therapy (HAART) exposure is limited. Although one small prospective study found fasting insulin levels increased among women and not men exposed to HAART,[48] another retrospective study found no sex association between the prevalence of diabetes mellitus and HAART exposure.[47] In a large clinical trial composed of primarily antiretroviral-experienced patients (n = 649, 24.9% women), the prevalence of diabetes also did not differ between men and women.[60]

Pernerstorfer-Schoen et al.[48] found men to have serum high-density lipoprotein (HDL) levels approximately 20% lower and low-density lipoprotein (LDL) : HDL were >40% higher than women. After HAART exposure, the LDL : HDL was no longer different between men and women because of increases in LDL levels in women. The authors concluded that women appeared to lose part of their 'natural protection' from arteriosclerosis after initiating HAART. Clark et al.[47] found that men had significantly higher triglyceride levels than women after PI exposure and El-Sadr et al.[60] also found that men were significantly more likely than women to have triglycerides levels >150 mg/dL in their predominantly antiretroviral-experienced population.

Objective measurements of body fat redistribution are generally only utilised in research studies and lipodystrophy diagnoses in clinical practice are often based on a patient's report and clinical exami-

nation. Although several studies have shown that women are at higher risk for body fat changes than men, this observation may be partially due to a gender difference in body awareness or the reporting of symptoms. The one cross-sectional study that evaluated body fat by a validated, objective methodology (dual-energy X-ray absorptiometry scanning) in 265 patients found that total weight and fat mass did not differ significantly in men and women with HAART exposure after adjustment for age, weight, race and exercise habits.[41] Regardless, studies have consistently suggested that the pattern of body fat redistribution is different between men and women. Women are more likely than men to experience truncal obesity and less likely to acquire subcutaneous fat wasting or atrophy that primarily occurs in the face and limbs.[38-45,61,62]

3. Conclusions

Women and men differ in various aspects that could influence their tolerance to HAART. Several studies have suggested that women are at higher risk for selected antiretroviral-associated adverse events than men. The aetiology for a sex difference in antiretroviral tolerance among non-pregnant adults is unknown, but possible contributing factors could include sex-specific physiological and hormonal influences or unique pharmacokinetic profiles. The influence of pregnancy may also increase the risk for selected toxicities.

Given that sex and pregnancy may influence antiretroviral concentrations, therapeutic drug monitoring (TDM) can be considered for selected individuals. US and European clinical pharmacologists recommend that TDM should be considered for specific scenarios in which PIs or NNRTIs are used. These scenarios include: clinically significant drug-drug or drug-food interactions; changes in pathophysiological states; patients such as pregnant women in which plasma concentrations may be lower than typical patients; and therapy in treatment-experienced patients, patients using alternative administration regimens, and antiretroviral-naive patients experiencing a lack of expected virological response.[22] However, information on relationships between PI and NNRTI concentrations and drug-associated toxicities is limited and relationships between NRTI concentrations and their intracellular pharmacologically active moieties have not yet been established.[22]

Antiretroviral adverse effects are a known barrier to adherence and can jeopardise the ability to achieve maximal virological suppression. Clinicians should be cognisant of the sex difference in adverse effect profiles for specific antiretrovirals between men and women and potential intolerance should be a critical component in discussions of HAART options in women. Further investigation of the potential associations between sex and antiretroviral-related intolerance or adverse effects is warranted.

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