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Review

Gender differences in the treatment of HIV infection

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ABSTRACT

In recent years, following the successful development of highly active antiretroviral therapy (HAART), several studies have evaluated potential differences between men and women in the course of HIV infection, response to treatment, and drug pharmacokinetics. A slightly lower HIV viral load in untreated women has been reported, particularly at higher CD4+ levels, but this difference does not translate into gender-specific recommendations concerning initiation of therapy. Data on drug response suggest similar response of treatment and similar outcomes in men and women, but female subjects appear to be more susceptible to adverse events related to antiretroviral treatment. Social and behavioural factors may determine gender differences in therapeutic adherence and treatment discontinuation.

The available evidence on pharmacokinetics of antiretroviral drugs suggests higher exposure in women compared to men. The factors and mechanisms more likely to be clinically relevant in determining this difference are represented by body weight and composition, renal clearance, and P-glycoprotein activity. Many antiretroviral drugs influence P450 activity, and interactions are common. The results of the studies exploring gender differences in pharmacokinetics of anti-HIV drugs are often not consistent, but several mechanisms may be involved in determining a final difference, and it might be difficult to adjust for all potential confounders. Specific considerations are needed in the selection of anti-HIV regimens in pregnancy, which must ensure protection from both HIV transmission and adverse neonatal outcomes.

In order to optimize treatment in all infected people with HIV, there is the need to conduct further research on gender differences in HIV therapeutics. To obtain this goal, specific studies should be designed and females' participation in both cohort studies and clinical trials should be promoted.

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1. Introduction: an epidemic increasingly affecting women

At the end of the year 2007 there were 33.2 million people estimated to be living with HIV, with an equal proportion of men and women infected [1]. On a worldwide scale, between 2001 and 2007, the ratio of men and women has remained globally stable, with similar increases in the total number of new infections occurring in men and women. However, in different parts of the world, the epidemic is increasingly feminine: in sub-Saharan Africa, the region most seriously affected by the epidemic, almost 61% of adults living with HIV in 2007 were women; in the Caribbean, in Latin America, in Asia and Eastern Europe the proportions of women living with HIV have also been growing in the most recent years.

Women have a greater biological vulnerability to HIV infection. Indeed, there is a higher (up to eight times) efficiency in male-to-female transmission [2], due to the greater exposed surface of the female genitalia, which can also suffer lacerations during the sexual act thus facilitating the entry of the virus. In addition to biological factors, however, in many parts of the world, gender inequality due to cultural, economic and social factors drives the feminization of the epidemics. Early sexual initiation, sexual violence, the use of sex as subsistence strategy, less knowledge on HIV because of educational inequalities, power-imbalanced relationships, are all factors that spread more heavily HIV infection among females, especially among poor and marginalized women.

2. Immunological, virological and clinical course of untreated infection: is it different in men and women?

Over the last 10 years several studies have evaluated possible differences between men and women in immunological and virological parameters of HIV infection. Discrepant results have been reported for CD4+ cell counts: both higher [3–7] and lower [8,9] CD4+ cell counts have been reported in women, while some studies have shown no difference according to sex [10–12]. In studies which assessed longitudinal trends, in some cases differences tended to persist over time, with similar CD4 slopes following infection in men and women [3,13,14], while in others a greater CD4 cell count decline was observed in women [9].

With respect to viral load, numerous studies have shown that women have lower viral load compared to men (between 25% and 80% lower HIV-RNA levels in women) [4–6,10,15–17]. It has been hypothesized that the different hormonal status of women and men may play a role in determining these differences. Lymphocyte function and cytokines production are affected by reproductive hormones [18], and tumor necrosis factor-alpha, which is associated with immune activation and increased viral replication, may be inhibited by estrogen, resulting in a lower viral load in women [19].

It has also been hypothesized that gender differences exist early in disease but tend to disappear with time. This is supported by the findings of Sterling et al., who demonstrated that gender difference in viral RNA levels decreased by 0.16 log per year, with the values converging 5.8 years after seroconversion [10]. This observed effect of time might also be mediated by the CD4 decline which occurs over the course of untreated infection. Two reviews on this topic suggest that, in general, the higher the CD4 cell count, the larger the HIV RNA female-to-male difference [20,21]. This hypothesis is also supported by the results of a recent large study, based on 1571 antiretroviral naïve persons (831 men, 740 women) with CD4+ <300/mm^3, enrolled in a randomized clinical trial, prior to initiation of ART, in 8 resource-limited countries and the US. Using a linear regression model that adjusted for other confounding factors, the study researchers found that there was a linear relationship between CD4+ cell count and viral load difference between men and women; the viral load difference between women and men

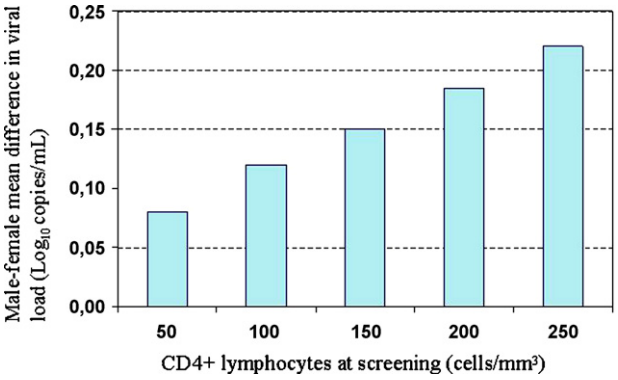

Fig. 1. Lower HIV plasma viral load level in women compared to men: estimated difference between men and women in mean $\log_{10}$ HIV-1 RNA levels at different CD4 cell counts. Adapted from Grinsztejn et al. [22].

was approximately 0.2 log among persons with CD4 cell count up to 300/mm^3 and less than 0.1 log among subjects with a CD4 cell count below 50/mm^3 [22], confirming that the male/female difference in viral load varied with CD4$^+$ lymphocyte count ($P = 0.04$), with the difference being greater at higher CD4 cell counts (Fig. 1).

The above virological and immunological differences, however, seem to have no clinical significance as measured by their impact on the progression of the disease. Earlier studies reported a reduced survival for women compared with men, but differences were due to different access to care [23,24]. The findings from cohort studies evaluating subjects with known dates of seroconversion suggest no statistically significant sex difference in rates of disease progression [10,16,25,26]. More recent studies have also shown that the effect of sex on progression to AIDS and death has not substantially changed after the introduction of HAART [27,28]. Very recently, Jarrin et al., analyzing by time period data from the CASCADE Cohort, found that, compared to no sex differences before 1999, women had a decreased risk of progression to AIDS (aHR 0.74, 95% CI 0.62–0.88) or death (aHR 0.68 95% CI 0.56–0.82) in the time interval between 1999 and 2004, despite a similar time on HAART [29]. This finding probably reflects the fact that in the general (uninfected) population in western countries women have a longer survival than men.

3. The physiological basis of gender differences in pharmacokinetics and response to antiretroviral drugs

Although several studies in human pharmacology have described differences in drug pharmacokinetics, in drug response and in drug toxicity between males and females, sex differences are difficult to ascribe to simple distinct mechanisms, due to the number of factors potentially involved and to the complexity of their interrelations (Table 1). Final differences in drug levels or in drug response can depend on sociocultural, psychoperceptual and behavioural factors, body size and composition, genetic, molecular or biochemical factors and hormonal/reproductive influences [30]. Cellular and animal models may generally only evaluate and control for a strict minority of such factors, and different mechanisms may be involved according to the drugs evaluated. The same problems apply to human studies in different therapeutic areas, and it may be very difficult if not impossible to control for all the potential factors involved in determining a final sex difference in pharmacokinetics or response to treatment.

Despite such limitations, some drugs have metabolic pathways in which significant differences between male and female subjects have been demonstrated. We will discuss in this section some of these differences which may be relevant for antiretroviral drugs,

Table 1
Factors potentially involved in determining sex differences in pharmacologic effects

- Body weight and composition, blood and organ volumes (e.g. bone mass)
- Absorption, intestinal motility and secretions
- Transport and distribution
- Protein binding and tissue affinity
- Metabolism: phase I (hydrolysis, reduction, oxidation, cyclization, decyclization)
- Metabolism: phase II (conjugation)
- Excretion (glomerular filtration rate, renal clearance)
- Intracellular metabolism
- Activity of drug transporters
- Differential (hormone-mediated) gene expression

Effect modifiers:
- Adherence
- Diet and nutritional factors
- Nutritional status
- Concomitant treatments
- Hormonal environment
- Reproductive status
- Smoking

together with the evidence available on specific sex differences demonstrated in the pharmacokinetics of antiretroviral drugs.

3.1. Body weight and body composition

Traditionally, differences between males and females have been ascribed to body morphology, size and composition. Differences in body weight alone may account for many and probably most of the observed sex-related differences in drug levels, drug response or toxicity, because the vast majority of drugs, with the antiretrovirals making no exception, are administered at the same dosage in all adult subjects irrespectively of sex and body weight.

In terms of relative organ mass, for most of the organs the differences between males and females are limited. Women, however, have a significantly higher relative amount of adipose tissue, and relatively lower skeletal muscle mass; blood and bone tissue are also slightly less represented in women compared to men. The higher content of body fat may expose women to a higher susceptibility to store lipophilic compounds and to differences in volume of distribution which can be clinically relevant. In women, the relatively larger volume of distribution for some lipophilic drugs may determine reduced C_{max}, increased $T_{1/2}$ and increased duration of effect [31].

3.2. Absorption

The differences in absorption between men and women are generally regarded as limited [31]. It should also be considered that potential sex-related differences in absorption might be dependent on several mechanisms, such as for example differential expression of enzymes involved in drug metabolism or sex-related differences in gastric emptying time or intestinal motility.

3.3. Metabolism

The differences observed between men and women in drug levels or response may be dependent on several metabolic processes. Phase I biotransformation of drugs mostly occur by oxidative reactions involving enzymes of the cytochrome P450 superfamily. The cytochrome P450 system (outlined in Table 2) consists of a large number of enzymes, classified in several families and

Table 2
Main enzymes of the cytochrome p450 system involved in drug metabolism

Isoenzyme	Characteristics	Examples of drug substrates	Anti-HIV drugs metabolised
CYP1A2	Relevant for the metabolism of some drugs. Few variant genes identified, but with a high interindividual variation in activity	Antidepressants, caffeine, NSAIDs, theophylline, warfarin	
CYP2A6	Mainly expressed in the liver. Genetic variants have been shown to influence its expression and/or activity	Nicotine, coumarine	
CYP2B6	Mainly expressed in the liver (3–5% of total hepatic microsomal P450); low expression also in intestine and other tissues. Involved in drug metabolism of many drugs. High interindividual variability, with some allelic variants involved in pharmacokinetic differences	Bupropion, cyclophosphamide, methadone, ifosfamide	Efavirenz (major role), nevirapine, nelfinavir
CYP2C8	Mainly expressed in the liver, it participates in the metabolism of some drugs	Cerivastatin, ibuprofen, paclitaxel	
CYP2C9	Mainly expressed in the liver, it is the main enzyme of the CYP2C subfamily (about 20% of the hepatic CYP content). Responsible for the metabolism of many commonly used drugs. Poor metabolisers represent a minority of subjects	Angiotensin II blockers, oral hypoglycemic agents, NSAIDs, antidepressants, warfarin, phenytoin	Ritonavir (minor role compared to CYP3A4), nelfinavir, etravirine
CYP2C19	Involved in hepatic drug metabolism, represents the main catabolic enzyme for some drugs	Proton pump inhibitors, antiepileptics, NSAIDs, antidepressants	Nelfinavir (major role), efavirenz, etravirine
CYP2D6	Second most important P450 enzyme for drug metabolism. Involved in the metabolism of about one quarter of commonly prescribed drugs. Genetic factors are responsible for important differences (largest phenotypical variability amongst the CYPs) among subjects (poor, extensive and ultraextensive metabolisers)	Antipsychotics, beta-blockers, antiarrhythmics, fluoxetine and other SSRI, tricyclic antidepressants, tamoxifen, vincristine	Ritonavir (minor role compared to CYP3A4), nelfinavir
CYP3A4	Abundantly expressed in liver. Most important member of the CYP3A subfamily, involved in the metabolism of about half of the commonly prescribed drugs. Also participates in the metabolism of some endogenous substrates. CYP3A activity exhibits marked ethnic and individual variability. Variant alleles encoding significantly altered activity are uncommon	Antineoplastics, benzodiazepines, antifungals, calcium channel blockers, tricyclic antidepressants, macrolides, statins, SSRIs, antihistamines, others	Predominant enzyme in the metabolism of most protease inhibitors; efavirenz (minor role), nevirapine, maraviroc
CYP3A5	Predominant hepatic expression. Similar substrate specificity with CYP3A4. Common homozygosity for nonproductive allelic variants	Nifedipine, cyclosporine, steroid hormones	Efavirenz, nelfinavir, saquinavir
CYP3A7	Mostly expressed in fetal life, with expression in adult life observed only in a very limited number of subjects. Role in drug metabolism probably limited		
CYP3A43	Very low levels of expression in human liver, uncertain role in drug metabolism		

NSAIDs: Non-steroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitors.

subfamilies. The P450 families most relevant for drug metabolism are CYP1, CYP2 and CYP3, which are mainly expressed in the liver. Extrahepatic (intestinal, in particular) expression, although lower, may also be relevant for the metabolism of some drugs. The level of enzymatic biotransformation may vary according to different gene expression or activity. Drug metabolism is affected in different ways, with common drugs acting often not only as enzyme substrates, but also as potential enzyme inducers or inhibitors, with frequent drug interactions responsible for changes in drug levels and consequent possible reduced drug activity or occurrence of drug-related adverse events. The main route of metabolism of antiretroviral drugs is summarized in Table 3. HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolised by the P450 system, mainly by CYP3A4 (with CYP2D6 and CYP2C9 also involved with a minor role in ritonavir metabolism, CYP2B6 and CYP2D6 also involved in nevirapine metabolism and CYP2B6 primarily responsible for efavirenz metabolism) [32].

There are limited data suggesting that sex differences in CYP450 activity or expression are clinically relevant. Some sex-based differences in enzyme activity have been reported for CYP1A2, CYP2B6, CYP2E1, and for CYP3A4 [31,33]. Sex hormones have been found to affect the activity of CYP2C19 [34], and differences in induction between males and females have been reported for CYP3A4 and CYP1A2 [35], but without a clear pattern. It is generally acknowledged that sex-related differences in activity of CYP450 are limited and that genetic (non X-linked) polymorphisms in the expression of CYP enzymes represent stronger determinants for clinically significant interindividual differences [31,36]. A precise definition of the role of sex-based differences in CYP-based metabolism is complicated by the effects of intersubject variability, ethnicity and age, and by the possibility that multiple enzymes of this family may be involved in metabolism of the same drug [31].

The finding that CYP3A4, which represent the main enzyme involved in drug biotransformation, seems to be less prone to genetic polymorphisms and sex-related differences [31], suggests a role for alternative mechanisms in determining the increased toxicity of antiretroviral drugs observed in women compared to men.

The activity level of P-glycoprotein, which shows an overlap in substrate specificity with CYP3A4, is increasingly considered as a potentially relevant factor, because sex-dependent differences in the expression of this drug transporter have been reported (with a lower expression in females). It has therefore been suggested that such differences, which may have clinical relevance, represent the actual determinants of some sex differences observed in the metabolism of some drugs, including HIV protease inhibitors, which are also metabolised by CYP450 enzymes [31–33].

Phase II biotransformation has the general function of producing polar conjugates which can better be cleared through the kidneys. It is represented by glucuroconjugation, acetylation, methylation or conjugation with sulfate, glutathione or amino acids. Sex-based differences in phase II metabolism may be potentially relevant in determining differences in pharmacokinetics, drug response and toxicity of different drugs. Animal models suggest in general higher activity and faster metabolism in males compared to females, and human studies suggest that genetic polymorphisms also may play a role. Many antiretroviral drugs (PI, NNRTI, NRTI) undergo phase II reactions before being eliminated in urine or bile. Zidovudine is metabolised by the UGT2B7 enzyme, which belongs to the uridine diphosphate glucuronosyl-transferases (UGT) family; this glucuronidation, however, is not reported as affected by sex differences [37].

It is generally accepted that men have slightly higher levels of renal clearance and glomerular filtration rate, even after correction for body weight. As a consequence, women might be characterised by a reduced elimination of compounds already metabolised through phase I and phase II biotransformation. This effect might be clinically relevant in determining higher plasma and/or tissue concentrations of antiretroviral drugs, predisposing women to a higher risk of adverse events.

3.4. Evidence for sex-related differences in HIV therapeutics

Several studies have indicated differences in toxicity of antiretroviral drugs between males and females, generally showing an increased risk for women. This has been described for rash, lactic acidosis, lipodystrophic changes, dyslipidemia and liver toxicity [38–42].

Similarly, a number of studies have shown sex-related difference in drug levels of antiretroviral drugs (reviewed in more detail by Ofotokun et al. [43]).

For nucleoside reverse transcriptase inhibitors, intracellular levels of phosphorylated nucleosides may represent a more accurate marker compared to plasma levels, because intracellular phosphorylation is an essential step in drug activation. Differences in activity of the cellular kinases responsible for nucleoside phosphorylation might determine differential efficacy and toxicity of the

Table 3
Anti-HIV drugs by pharmacological class and metabolism [62]

Drugs	Main route of metabolism
Nucleoside/nucleotide reverse transcriptase inhibitors	
Abacavir (ABC)	Hepatic metabolism through alcohol deidrogenase and glucuronyl transferase. Subsequent renal excretion of metabolites.
Didanosine (ddI)	Renal excretion by glomerular filtration and active tubular secretion
Emtricitabine (FTC)	Renal excretion. Limited (<10%) oxidation and glucuroconjugation
Lamivudine (3TC)	Renal excretion
Stavudine (d4T)	Renal excretion
Tenofovir (TDF)	Renal excretion (filtration and active tubular transport)
Zidovudine (AZT, ZDV)	Glucuronidation (glucuronyl transferase UGT2B7), renal excretion (glomerular filtration and active tubular secretion)
Non-nucleoside reverse transcriptase inhibitors:	
Delavirdine (DLV)	P450 (CYP3A4)
Efavirenz (EFV)	P450 (CYP3A4, CYP2B6)
Etravirine (ETV)	P450 (CYP3A4, CYP2C9, CYP2C19)
Nevirapine (NVP)	P450 (CYP3A4, CYP2B6)
Protease inhibitors[a]:	
Atazanavir (ATV)	P450 (CYP3A4)
Darunavir (DRV)	P450 (CYP3A4)
Fosamprenavir (fAPV)	P450 (CYP3A4)
Indinavir (IDV)	P450 (CYP3A4)
Lopinavir (LPV)	P450 (CYP3A4)
Nelfinavir (NFV)	P450 (CYP3A4, CYP2C19, CYP2C9, CYP2D6)
Ritonavir (RTV)	P450 (CYP3A4, CYP2D6)
Saquinavir (SQV)	P450 (CYP3A4)
Tipranavir (TPV)	P450 (CYP3A4)
Fusion inhibitors:	
Enfuvirtide (ENF, T-20)	Catabolism to amino acids
Integrase inhibitors:	
Raltegravir (RAL)	Glucuronidation (glucuronyl transferase UGT21A1)
CCR5 inhibitors:	
Maraviroc (MVC)	P450 (CYP3A4)

Note: The following fixed dose combinations are also commercially available: zidovudine plus lamivudine; abacavir plus lamivudine; abacavir plus lamivudine plus zidovudine; tenofovir plus emtricitabine; efavirenz plus tenofovir plus emtricitabine.

[a] Usually administered with low dose ritonavir.

drugs involved. Some pharmacokinetic studies have investigated this issue, suggesting the presence of sex differences. Aweeka et al. found significantly higher concentrations (as area under the concentration versus time curve) of zidovudine monophosphate and zidovudine triphosphate in men, with no differences between men and women in zidovudine plasma concentrations [44]. Conversely, Anderson et al. [45] reported significantly higher intracellular concentrations of zidovudine and lamivudine triphosphate in women compared to men (ratios of 2.3 for ZDV and 1.3 for 3TC); higher intracellular levels of total phosphorylated zidovudine in women were also found in a different study by Stretcher et al. [46], but both studies included a limited number of women.

Sex-related differences in the activity of the cellular kinases responsible for nucleoside phosphorylation might explain, at least partially, the increased susceptibility of women to NRTI toxicity. No conclusive evidence, however, is available to confirm this hypothesis, and further studies evaluating potential sex differences in the activity of cellular kinases involved in NRTI phosphorylation would be important.

Some studies have also compared drug levels in women and men receiving non-nucleoside reverse transcriptase inhibitors. Despite evidence of a particular sensitivity of females to NNRTI toxicity, the investigations on plasma drug levels of nevirapine and efavirenz have shown conflicting results, with some studies indicating higher levels or lower clearance in women for nevirapine [47], no sex-related differences in pharmacokinetics of this drug [48,49], limited differences for efavirenz, not requiring dose adjustments [50], and higher efavirenz levels in women [51].

Some evidence also exists for sex-related differences in the pharmacokinetics of protease inhibitors. Higher saquinavir concentrations and lower weight-adjusted saquinavir clearance in women were reported by Fletcher et al. [52]; Pai et al. showed higher exposure in women, with higher saquinavir $AUC_{0-24\,h}$ and lower ritonavir clearance [53], a finding also confirmed by Ribera et al. [54]; Trout et al., however, did not find any association between sex and SQV AUC in patients with and without weight loss and diarrhea [55]. Some studies on indinavir also reported higher exposure in women, as measured by proportion of women with high drug levels [56], and by measures of oral clearance [57]. Other studies, however, failed to demonstrate significant sex differences in indinavir exposure [58] or lopinavir/ritonavir plasma concentrations [59]. Higher levels of saquinavir, ritonavir and atazanavir after adjustment for body weight were found in women in a study of seronegative volunteers receiving either saquinavir/ritonavir or saquinavir/atazanavir [60].

Data on the newer antiretroviral drugs based on different mechanisms of action are limited. Enfuvirtide is an HIV fusion inhibitor which must be administered subcutaneously because of a peptidic structure. The drug has a limited volume of distribution and its clearance appears to be influenced by sex and bodyweight, but with no need for dose adjustments and no apparent effect of gender on efficacy and safety [61]. Raltegravir is primarily eliminated by glucuronidation mediated by the UGT1A enzyme, while maraviroc is a P450 CYP3A substrate.

Taken together, the available evidence on antiretroviral drugs and sex differences in pharmacokinetics suggest higher exposure in women compared to men. Not all the studies, however, have consistently demonstrated such an effect, and the statistically significant differences observed should be weighted in terms of clinical relevance. Based on current evidence, the factors and mechanisms more likely to be clinically relevant in determining sex differences are represented by body weight and composition, renal clearance, and P-glycoprotein activity.

All the above conclusions should also be considered cautiously because not all the possible confounders potentially involved have been considered in adjusted analyses. Although adjustment for body weight and age is feasible, it might be difficult if not impossible to adjust for other mechanisms potentially involved, such as expression of P-glycoprotein and other drug transporters [31,33], expression of phase I and phase II metabolising enzymes [43], activity of cellular kinases, and pharmacoenhancement by ritonavir, which is commonly coadministered as a booster in most of the recommended therapeutic schedules. Further studies may help defining to what extent the observed differences between men and women in pharmacokinetics and toxicity of antiretroviral drugs may be related to gender differences in the pharmacogenomics of metabolising enzymes and drug transporters.

4. Women and HAART

Since the introduction of highly active antiretroviral therapy (HAART), conflicting results have been reported about potential gender differences in several aspects of HIV therapeutics, which include: time of initiation of antiretroviral therapy, virologic and immunologic response to HAART, therapeutic adherence and adverse reactions to antiretroviral drugs. It is however important to keep in mind that, despite the gender-related differences observed in some studies, current guidelines [62] state that the indications for initiation of therapy and the goals of treatment are the same for HIV positive women and men. Similarly, criteria for changing antiretroviral regimen are uniformly applied to males and females. Specific issues are developed below.

4.1. Time of initiation of HAART and determinants of treatment

Potentially, the observed gender differences encountered in viral load during the natural course of HIV infection might affect treatment decisions, creating differences between men and women in timing of start of treatment. Overall, the results of the studies which have investigated this issue are not homogenous: in a French cohort involving 5735 patients from 62 French hospitals, no gender differences were found in the time interval between enrolment and HAART initiation during chronic infection [63]. In agreement with this study, the results of the Italian ICoNA cohort showed a longer median time to start of HAART among women compared to men, but this difference was not significant in adjusted analyses [64]. Data collected from US HIV primary care sites showed male gender to be significantly associated with an increased likelihood of HAART initiation during chronic infection [65]; similarly, female sex was associated with a decreased likelihood of HAART prescription in a large cohort of US patients [66] and in a review of medical and pharmacy records of US HIV positive subjects [67]. Even after controlling for disease severity, HIV risk factors and race/ethnicity, women were less likely to receive HAART than men in all analyses.

It has been suggested that such differences could partly depend on the lack of adjustment for other indicators of socio-economic status, such as education or income, that are strongly correlated with gender among patients with HIV disease in the US. Sayles et al. [68] observed that women had greater difficulties in taking medications openly compared with homo/bisexual men and that this was associated with a lower probability of being on HAART in an adjusted model. Socio-economic and cultural gender-related factors seem therefore to play a relevant role in determining assumption of therapy. In resource-limited settings, evidence from over 50 low and middle-income countries suggest that the ratio of men to women receiving treatment is overall in line with regional HIV prevalence sex ratios. Actually, in most Southern African countries, proportionally more females are on HIV antiretroviral treatment than men, even when the higher HIV infection preva-

lence in females is accounted for [69]. The programs encouraging women to attend antenatal clinics in an effort to reduce vertical transmission may be responsible for this effect, contributing to a higher access of women to HIV care services in resource-limited countries.

4.2. Antiretroviral drugs and regimens

Recommendations regarding the choice of an antiretroviral regimen for HIV infected women are subject to a number of considerations, including the already mentioned gender related differences in drug bioavailability, distribution and metabolism, and potential untoward effects of drugs on pregnancy outcome for women of reproductive age. The latter issue is covered in a separate section of this article.

Gender-dependent differences in susceptibility to adverse events are common and are largely attributable to the previously described mechanisms. NRTI-related lactic acidosis is a severe, life-threatening complication of NRTI treatment which appears to be more frequent in women [70], especially if obese. The non nucleoside reverse transcriptase inhibitor nevirapine is also responsible for more frequent side effects in women than in men: a nevirapine-related rash has been observed in 9.5% of women but only in 1.1% of men [71], and nevirapine-associated hepatotoxicity is also more common in women, especially if they have high CD4 cell count [72]. In fact, rash and hepatotoxicity are often seen together as part of a hypersensitivity reaction, usually occurring in the first 8 weeks of treatment with nevirapine. On this basis, it is now recommended not to start regimens which include nevirapine in women with more than 250 CD4 cells/mm^3 [62]. Hypersensitivity reactions to other, non nevirapine-based, HAART regimens are also more frequent in women [73]. Body fat redistribution, a commonly occurring side effect of treatment in patients on long-term antiretroviral therapy, also follows a sex-specific pattern, and females are more susceptible to lipodystrophy and metabolic abnormalities [74].

4.3. Immunologic and virologic response to HAART

As already mentioned, all the information available on women with HIV/AIDS suffer from the limited number of women enrolled in clinical studies, in comparison with the male population. To partially compensate for this limitation, cohorts of HIV positive women have been established throughout the world, one of the largest being the WIHS (Women Interagency HIV Study) cohort, which currently includes more than 3700 US women (of whom almost 1000 HIV uninfected). Despite some conflicting results, overall no gender-related differences have been observed in terms of virological and immunological response to HAART. Fardet et al. observed that the probabilities of achieving a CD4 increase of at least 100 cells/mm^3 and a viral load below 500 copies/ml were similar in men and women [63]; conversely, female sex was associated with higher and sustained CD4 gain in an observational trial conducted in US [75]. In contrast, in an Italian cohort study of 2460 HIV positive individuals, no sex differences were reported in terms of proportion of patients achieving viral suppression or recovering CD4 cell count from baseline [5]. Similarly, a study conducted within the EuroSIDA cohort failed to demonstrate significant differences between males and females regarding response to HAART, although women appeared at higher risk of virological rebound [76]. Such a trend towards an increased rate of virologic rebound among women was observed in different trials, but in no cases it appeared to be independently associated to female sex in adjusted analysis [77].

In recent years several clinical studies have tested feasibility, safety and outcomes of structured HAART interruptions, e.g. planned discontinuations of antiretroviral treatment in subjects who have achieved plasma HIV-1 levels below the threshold of detectability. These interruptions are performed following two main approaches: CD4-based (with different CD4 cell count thresholds for stopping and reinitiating treatment) interruptions, and intermittent HAART, with different predefined duration of "on-" or "off-" treatment periods. Overall, published studies do not suggest significant gender-related differences in response to HAART interruptions; however, considering individual trials, discordant data have been produced. In the ANRS 100 PRIMSTOP study, female sex was an independent predictor of virological response [78]; in the DART trial, conducted in central Africa, women had a 2.3-fold higher virological response compared to men [79]. Finally, in the ISS PART, male sex independently predicted response to intermittent HAART in terms of CD4 cell count and adherence to study protocol [80]. Different study designs and populations are likely to account for these apparently discordant results.

Since HIV infection is mainly transmitted by sexual route, reducing viral load in the genital tract is an essential aspect of HAART, strictly related to the penetration of antiretroviral agents in this compartment. This issue is also relevant for identifying the most suitable agents for pre- and post exposure prophylaxis. The most recent studies conducted to compare drug concentrations in plasma and cervicovaginal fluid showed that all anti HIV agents can be rapidly detected in the female genital tract after an oral dose, with notable differences: lamivudine, emtricitabine, zidovudine and tenofovir achieved higher concentrations in the genital tract compared to plasma (and are therefore attractive candidates for oral pre- and post-exposure prophylaxis), whereas stavudine, abacavir, and efavirenz achieved genital tract exposures less than 10% of blood plasma and should therefore not be considered for these purposes. Atazanavir and lopinavir achieve low genital tract concentrations but due to their favorable therapeutic indexes partly compensate for this limited penetration [81]. Very recently, it has been reported that one of the newest antiretroviral drugs, maraviroc, an inhibitor of HIV entry, achieves very high levels in the female genital tract, higher than those measured in plasma, suggesting its potential role for HIV prophylaxis [82].

4.4. Treatment adherence and discontinuations

An association between female gender and reduced rate of adherence to antiretroviral medications has been reported. In a study assessing the 1-year virologic response to antiretroviral therapy in 739 subjects (female: 92), women were significantly less likely to be adherent to therapy (34.8% versus 62.9%; $P < 0.001$) than male participants, and this was responsible for the observed difference in the HIV RNA response rate (46.7% versus 64.8% with HIV RNA < 500 copies/ml at 1 year) [83]. In a subsequent study performed in 970 patients (women: 126) on first-line antiretroviral treatment, female gender was associated with more rapid rebound rates in univariate analyses (RH = 1.39, 95% CI 1.05–1.82), but the effect of gender was no longer significant after adjustment for other covariates, including adherence (aRH = 0.95, 95% CI: 0.71–1.28) [84]. The finding was explained by the higher proportion among women of history of injection drug use, a condition significantly contributing to incomplete adherence among patients with HIV. A different study, aimed to assess the behavioral correlates of adherence, confirmed the above hypothesis, showing no gender differences in adherence rate, with age and current use of injection drugs significantly associated with adherence in a multivariable analysis [85]. Several other studies did not show any gender difference regarding treatment adherence [7,86].

Women have also been reported to undergo more frequently treatment discontinuations during antiretroviral therapy. In a large

cohort study (1551 subjects) with a high representation of women, designed to investigate the predictors of treatment discontinuation in clinical practice, among the 222 subjects who had a discontinuation, women were more likely to have a discontinuation than men in a multivariate analysis (HR = 1.61, 95% CI: 1.15–2.27) [87]. These findings were confirmed in other cohorts [88]. The reasons for this occurrence are not clear. The main possible explanation was a lower adherence to HAART in women compared with men, mainly explained by social and behavioural factors. Sex differences in occurrence of drug-related adverse events [89] could be an alternative explanation of this observed difference.

Overall, available evidence suggests that a specific association between gender and treatment adherence or treatment discontinuations is unlikely, but social and behavioral aspects may play an important role in these issues.

5. Pregnancy and antiretroviral treatment

5.1. Efficacy and safety

Therapeutic issues in pregnant women with HIV are subject to unique efficacy and safety considerations. Antiretroviral treatment in pregnancy is recommended irrespectively of clinical, immunologic and virologic maternal status, because of its established role in reducing vertical transmission of HIV. In the presence of all preventive interventions (antiretroviral treatment, cesarean delivery and selection of formula feeding), the risk of vertical transmission decreases from about 20–25% to less than 2% [90–92].

The need to administer antiretroviral therapy to all pregnant women with HIV must however be balanced against the risks of maternal and neonatal adverse outcomes. Since the demonstration of efficacy of zidovudine (administered as oral antenatal treatment to the mother plus intravenous intrapartum treatment and oral treatment to the newborn) in preventing HIV vertical transmission [93], treatment guidelines have significantly evolved, with several possible scenarios associated to distinct recommendations. Treatment guidelines differ according to the socioeconomic context, and simplified regimens are often recommended in countries with limited resources. In countries with adequate resources, administration of HAART currently represents the standard of treatment for pregnant women with indication to treatment for maternal health [94–96], using regimens and agents which are expected to minimise both maternal and neonatal risks. In women with no immediate need of antiretroviral treatment for their own health, some guidelines [96] consider less aggressive treatment, which however might favour development of viral resistance. Important individual limitations exist for the use of antiretroviral drugs in pregnancy: efavirenz use during first trimester is contraindicated because of birth defects observed in primates and humans; the combination of stavudine and didanosine should be avoided because of observed cases of severe and sometimes fatal lactic acidosis; nevirapine should not be started in women with more than 250 CD4 cells/mm^3 [94]; finally, some concerns exist for tenofovir use, because of potential negative effects on metabolism of the developing bone [95].

It should also be considered that among women with HIV only a minority of pregnancies are planned, a situation which determines high therapeutic variability and common occurrence of ongoing treatment with contraindicated drugs at conception, which leads to frequent changes of regimen during pregnancy [97].

For some drugs, sufficient data have been collected to exclude an increase in overall birth defects greater than 1.5-fold (lamivudine and zidovudine) or greater than 2-fold (abacavir, efavirenz, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine and tenofovir). An increased risk of birth defects, of uncertain explanation, has been observed for didanosine (overall prevalence of defects among cases with first trimester exposure: 5.3%, compared to a general rate of 2.8 for any antiretroviral therapy) [98].

Birth defects, however, do not represent the only concern in terms of potential negative consequences of antiretroviral treatment in pregnancy: based on early reports, children antenatally exposed to nucleoside analogues (zidovudine, with or without concomitant lamivudine) might be at risk of severe clinical manifestations of mitochondrial disease [99]. Subsequent confirmatory studies have shown that this occurrence, at least in terms of significant clinical disease, is probably rare [100–101].

Another important and rather controversial issue is represented by the role of antiretroviral treatment in favouring preterm delivery. Early studies conducted in US and European women were not consistent, with only the European cohorts showing an association between combination antiretroviral treatment (particularly with protease inhibitors) and premature delivery [102–104]. More recently, this association was confirmed in other studies from both US and Europe, where the rate of premature delivery before 37 weeks is about 25% [105–108].

Finally, therapeutic choices in pregnancy should consider the possibility that antiretroviral therapy might precipitate or exacerbate different pregnancy-related conditions, such as abnormalities of carbohydrate metabolism and diabetes, preeclampsia, cholestasis and fatty liver. Use of those drugs whose toxicity profile overlaps the above clinical conditions should therefore be implemented cautiously, taking appropriate measures in clinical and laboratory monitoring.

5.2. Pharmacokinetics of anti-HIV drugs in pregnant women

Pregnancy is characterised by important physiologic changes that affect drug disposition: total body water, plasma volume and body fat compartment increase significantly, changing the distribution of both hydrophilic and lipophilic drugs. Protein binding is reduced by the concomitant occurrence of reduced albumin concentrations and competitive inhibition from steroid hormones, which also reduce intestinal motility and increase gastric and intestinal transit time. Renal plasma flow and glomerular filtration rate also increase, determining a faster renal drug clearance.

At a molecular level, changes in activity of enzymes involved in phase I and phase II biotransformation have been described [31]. The effects of pregnancy on the activity of the enzymes of the CYP P450 system are heterogeneous, with some enzymes showing increased (CYP2C9, CYP2D6, CYP3A4) and others decreased (CYP1A2, CYP2C19) activity. Pregnancy might also increase the activity of glucuronidating enzymes, with a potentially faster clearance of the drugs which are predominantly metabolised through this route.

Most of the available pharmacokinetic data on the use of antiretroviral treatment in pregnancy refer to protease inhibitors and nevirapine. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors act not only as substrates for CYP P450 enzymes, but also as inducers or inhibitors, with complex effects in the case of concomitant administration. Reduced exposure during pregnancy has been observed for nevirapine [109] and for different protease inhibitors, including indinavir [110,111], saquinavir [112] and nelfinavir [113–115] when used without concomitant ritonavir. The concomitant administration of low-dose ritonavir was associated to exposure levels comparable to the postpartum period for saquinavir and atazanavir [116–118], but pregnant women taking lopinavir/ritonavir had reduced exposure to lopinavir compared to postpartum and to historical controls [119]. An enhanced CYP3A4 activity during pregnancy has been suggested as a possible cause of lower levels of protease inhibitors during pregnancy, but given the

complexity of the mechanisms potentially involved, it might be difficult to ascribe differences in pharmacokinetics between pregnant and non-pregnant women to specific mechanisms.

6. Conclusions

In HIV therapeutics, as in other fields, gender represent an important determinant of interindividual differences in pharmacokinetics, treatment adherence, and susceptibility to adverse events. Several aspects still remain unsolved and there is the need to better define the determinants of the above differences. In order to obtain this goal, both cohort studies and clinical trials should ensure adequate representation of women in clinical research, and study protocols should be carefully designed to take into account in their methodology the complexity of the factors potentially involved in determining a final gender difference. An increasing attention paid to this subject is likely to translate into a better individualisation of treatment and better efficacy and safety outcomes for both existing and new antiretroviral agents. Females' participation in clinical trials should be promoted and HIV positive women should be informed about the importance of volunteering for such studies.

Conflicts of interest

The authors do not have a commercial or other association that might pose a conflict of interest.

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