Title: **Out of focus: tailoring the cascade of care to the needs of women living with HIV**

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Short title: European focus on specific needs of women living with HIV

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Abstract

Around half of the global adult HIV-positive population are women, yet historically women have been under-represented in clinical studies of antiretroviral therapy (ART) and there had been minimal exploration of gender-specific factors related to the response to and appropriateness of treatment choices in women living with HIV (WLWH). There are several key issues that pertain to the cascade of HIV care that make it important to differentiate WLWH from men living with HIV. Factors that are gender specific may impact on the status of WLWH, affecting access to diagnosis and treatment, optimal clinical management, ART outcomes, retention in care, and the overall long-term wellbeing of WLWH. In this review, we discuss the results of recently reported women-only clinical trials and highlight the key unmet needs of WLWH as they pertain to the cascade of HIV care across World Health Organization European region countries. As significant knowledge gaps remain, the review identifies key areas where further research is required, in order to support improved management of WLWHand guideinformed clinical decision-making, including addressing psychosocial factors as part of comprehensive care.

# Introduction and epidemiology overview

Women make up almost 50% of adults living with HIV worldwide and globally in 2015 27% of new HIV diagnoses were in women aged 25 years or older and a further 20% were in women aged 15–24 years (Figure 1a). 1,2 European surveillance data from the European Centre for Disease Prevention and Control (ECDC) for 2015 showed that 1 in 3 new HIV diagnoses were in women, with new diagnoses in women occurring at a rate of 2.6/100,000 in the nations comprising the European Union and European Economic Area (EU/EEA) and at a rate of 4.4/100,000 for the countries comprising the World Health Organisation (WHO) European Region. 3 Marked differences in the rate of new cases of HIV in women can be seen between regions of Europe (EU/EEA) and ECDC-WHO countries covered by the European Surveillance System (Figure 1b). The male-to-female ratio of new HIV cases also varies according to country – the overall ratio was 3.3 in the EU/EEA and 2.3 in the WHO European Region. Modes of transmission also vary by country. In women, transmission of HIV is most often from an HIV-positive sexual partner. Women described as migrant are at particularly high risk of HIV acquisition, with a proportion of migrants acquiring HIV after arrival in the EU/EEA. 3 Transmission through injecting drug use (IDU) has decreased overall in recent decades, yet IDU still accounts for more than a quarter of the reported new HIV diagnoses in Eastern Europe. Recent European statistics also show that the highest crude specific rate of new HIV diagnosis in women was in those aged 25–29 years old (e.g., 6.7/100,000 for the EU/EEA), identifying young women as an especially vulnerable group. 3 New HIV infections do occur in older women, however, including women aged 50 years and older. 1,3

Effective combination antiretroviral therapy (ART) has transformed HIV into a chronic disease of survivorship. Today, people living with HIV (PLWH), including women, who are well managed and successfully treated, can achieve near-normal life expectancy. 4-8 Early diagnosis, prompt ART initiation, and optimal management of comorbidities are important determinants of favourable disease outcomes and improved life expectancy amongst PLWH, including both men and women (Figure 2). 6,7 UNAIDS aspires to fast-tracked improvements in global HIV control by 2020, with a target for 90% of patients knowing their HIV status, 90% being on ART, and 90% showing virological suppression. 9 Yet, in Europe, around 48–60% of PLWH are diagnosed late (i.e., CD4 count <350 cells/mm3), and there remains a need to determine which HIV testing strategies may be required to reduce the number of late diagnoses for women. 9-11

Barriers to HIV testing, whether real or perceived, often delay or prevent access to care for women. 12 Women living with HIV (WLWH) face a unique set of social and stigma-related issues pre- and post-diagnosis, including gender-based power imbalances, risk of violence, fear of disclosure, racism, and sexism, which contribute to the late diagnosis of HIV. 13-16 In addition, poverty, immigration issues, lack of education and socio-cultural factors have unique impacts on WLWH and affect their clinical outcomes. 17 The issues faced may evolve over a woman’s lifetime, from adolescence into adulthood, to the stage of ageing with HIV. Women typically encounter more opportunities for accessing medical services over their life-course than men (e.g., in relation to reproductive needs, childbirth, cervical and breast cancer screening), and these contacts with medical services may be missed opportunities to diagnose and connect with WLWH.

Gender-specific factors can also impact on the clinical care of WLWH post-diagnosis – affecting access to and retention in care, management, and likelihood of achieving and maintaining viral suppression on ART (Table 1). 12,17-22 In addition to female-specific challenges around reproductive considerations, pregnancy and menopause, women differ from men in body composition and pharmacokinetic (PK) parameters. Such differences could be expected to influence therapy choices, treatment success, tolerability and toxicity, and overall ability to cope with the treatment. 17,22

In this new era, HIV management is undergoing a paradigm shift, with increased emphasis on prevention, and a focus on optimising the cascade of HIV care and the long-term wellbeing of PLWH. 23 Increased efforts and specific considerations are required to address the additional health issues associated with the unique factors, comorbidities, and ageing-related issues that WLWH face today. 24,25 For this reason, we have conducted a scoping review to highlight some of the key issues pertaining to the cascade of HIV care that make it important to differentiate WLWH from men living with HIV.

# Methods

We used scoping review-informed methodology to help identify and describe key issues experienced by WLWH as they pertain to the cascade of HIV care. 26 During the process of identifying relevant studies, we reviewed the literature in order to refocus on more specific searches. The following five steps were included: 1) identifying the research questions, 2) identifying relevant studies, 3) study selection, 4) reviewing the data, 5) collating, summarising and reporting the results of the literature review. In this study, MEDLINE was searched for articles published from 1980 to 2016 using diverse Medical Subject Headings (MeSH) for each section, including “HIV”, and “women” or “female”, together with strings of “cascade of care”, “HIV testing”, “linkage to care”, “retention in care”, “antiretroviral therapy”, “drug adherence”, “antiretroviral response”, “antiretroviral interactions” and “antiretroviral toxicity”. The abstracts of potentially relevant papers were scanned to determine their importance for the review overall and the papers that best represented the topics were chosen for more in-depth review. In addition to this literature scoping, we included a review of papers and communications, which we as an author group considered offered additional insights on care of WLWH. We also reviewed the recent literature on clinical studies of ART regimens in WLWH and considered aspects of women’s general health and wellbeing (e.g. reproductive healthand management of the menopause) in relation to challenges facing WLWH.

# Results and Discussion

At the time of the review, there were 165,000-plus papers mentioning the term “HIV” and of these, fewer than 5% mentioned the word “female” or “women”. For the search terms of “HIV” plus “women or female” searched together with the following strings, the references found numbered: three for “cascade of care”, 470 for “HIV testing”, nine for “linkage to care”, 16 for “retention in care”, 355 for “antiretroviral therapy”, three for “drug adherence”, 13 for “antiretroviral response”, one for “antiretroviral interaction” and two for “antiretroviral toxicity”. After removal of duplicate citations, there were 846 abstracts to scan. These captured abstracts and other literature relating to management and care of WLWH were divided into four sections on: 1) HIV testing and linkage to care, 2) HIV disease pathogenesis, 3) ART use, adherence and virological response, and 4) ART trials that recruited only women. We conclude our discussion with a section reviewing the gaps in knowledge and research needs in the field.

## HIV testing and linkage to care

With almost half of all new HIV diagnoses in Europe made late, 3 attitudes to HIV testing should be scrutinised in the European female population. Current guidelines recommend the routine offer of HIV testing to women who are pregnant; diagnosed with a sexually transmitted infection; with an HIV-positive partner or with a partner at high risk of acquiring HIV (such as IDUs, or men who have sex with men); who are themselves IDUs; who are sex workers; and who originate from countries with a high HIV prevalence. 27,28 These recommendations potentially miss opportunities to offer HIV testing at other times when women may be in contact with healthcare services – such as when seeking contraceptive advice, accessing termination of pregnancy services, undergoing smear tests or breast screening. 29 The HIDES 2 (HIV Indicator Diseases Across Europe Study – phase 2) audit of HIV testing shows that routine, opt-out testing of pregnant women has been easily introduced and met with high acceptance rates in many settings, possibly reflecting the added value for the mother of also potentially protecting the unborn child. 30 In Russia, in settings of high HIV prevalence, women applying for medical care are all tested for HIV, and this initiative has been shown to increase timely detection of HIV. [I Latysheva, personal communication, Republican Clinical Hospital of Infectious Diseases of Ministry of Health Russian Federation, St Petersburg, Russia] National testing campaigns were also organised recently in Russia, to specifically target this population. Campaigns across ten regions used trained female students, outreach personnel and volunteers, with the aim of helping women overcome the fear of testing. Of the women testing positive for HIV in these campaigns, only 30% were previously aware of their HIV status. [I Latysheva, personal communication]

Targeted testing of women considered to have high-risk behaviours, or who come from places with a high HIV prevalence, may be resented and seen as stigmatising. 31 Some women may view volunteering for testing as implying suspected infection, some may have incorrect perceptions about their risk of HIV, and others may fear the diagnosis: all factors that can serve as important barriers to coming forward for, or accepting the concept of HIV testing. 32

Public health initiatives across Europe that aim to target at-risk individuals with or without HIV-indicator conditions have helped to highlight some of the barriers preventing WLWH from accessing testing and care. For example, the HIDES I study highlighted inherent staff biases towards offering HIV testing to women, and the importance of improving our understanding of why people refuse testing. 33 Negative assumptions and fears about HIV, including the fear of negative reactions from others, are recognised barriers to testing. 13,15,32 Surveys suggest some health care professionals (HCPs) may find it difficult to address the subject of HIV testing with adolescents and adults. 34 HCPs need to be aware of these barriers and any barriers they may themselves be inadvertently placing in the way of encouraging WLWH to engage with care.

Importantly, stigma and discrimination are reported amongst WLWH more frequently than in men living with HIV, and may contribute to the lack of or delay to HIV testing amongst women. 17,35 Women may especially fear disclosure if found to be HIV positive, more so if they come from communities with significant gender power inequities; they may have fears about HIV in general and choose not to be tested.17

Testing delays may also be due to the fact that women may not appreciate their risk for HIV or lack knowledge of the benefits of successful ART. 36 The setting also impacts upon testing, and subsequent linkage and access to care. Most HIV testing takes place at HIV centres, and genito-urinary medicine clinics. HIV testing occurs less often and results may take longer in general practitioner/family practice settings, tuberculosis services, or non-governmental organisations. 16 Testing technologies permitting point-of-care testing may help reduce stigmatisation and allow easier access to HIV testing, particularly when targeted at women in the community.

## HIV disease pathogenesis

There appear to be gender-related differences in susceptibility to HIV infection and in key virological and immunological parameters following infection with HIV (Table 2). The literature reports that untreated HIV-positive women have lower plasma HIV-1 RNA levels than do untreated HIV-positive men, even early in infection, and may have higher CD4 cell counts. 37-41 A meta-analysis found that, after adjustment for CD4 cell counts and prior to starting ART, women have on average 41% lower viral load levels than men. 42 Findings from the START study (Strategic Timing of AntiRetroviral Treatment study) are consistent with the older reports. It has been postulated that the premenopausal hormonal environment may limit HIV replication, 40 and it has been documented in a well-matched cohort of ART-treated, virally-suppressed premenopausal women and men, that multiple measures of virus activity and immune activation/exhaustion were lower in women despite comparable frequencies of CD4+ T cells harbouring HIV DNA. 43 However, the current literature continues to suggest that these virological and immunological differences do not translate into appreciable benefits for women in terms of disease progression. 19,40,42

## Antiretroviral use, adherence and treatment response amongst WLWH

Gender differences have not been a major focus within HIV research until recently. As a result, perhaps surprisingly, a similar management approach is followed to treat women and men. Guidelines on the use of ART do not contain guidance on gender-specific treatment choices. 28,44 The agencies that have released these guidelines do have separate guidelines or sections on the use of ART in pregnancy, although these are not always entirely consistent with their general HIV treatment guidelines.

WLWH and men living with HIV may experience gender differences in terms of time to initiation of treatment and with regards to choice of treatment. For example, data from two multicentre cohorts in Spain – one from the period 1996–2004 and the other for 2004–2008 – showed that, by competing risk analysis, women started ART earlier than men in the 2004–2008 cohort and, in both cohorts, women showed a shorter time to the first change of ART than men. 19 Such data also highlight that there can be differences between cohorts and temporal differences in practices. The START trial, which evaluated initiation of therapy in HIV-positive patients with CD4 counts higher than 500 cells/mm3, provides evidence for the recommendation that treatment should begin as early as possible following diagnosis, regardless of CD4 cell count. Women made up 27% of the population.45 In this study across all subgroups, hazard ratios consistently favoured the immediate-initiation subgroups and, although no statistics are reported for gender, there was a reported lower rate of endpoint events for immediate initiation of ART in women (0.42 per 100 person years) compared with men (0.66 per 100 person years), with endpoint data suggesting immediate initiation of ART may be better than deferred ART in women, with less of a difference in men. 45

Guidelines clearly support test and treat strategies – early initiation of treatment from the time of diagnosis. 28,44 However, we are yet to fully determine what specific factors – if any – are important to consider when initiating treatment in WLWH, as we elaborate in this review. What is more, our review of the literature makes clear that more research is required to collect representative datasets that can effectively inform guidelines, and to develop core standards of care specific to the needs of WLWH. One problem with formulating standards–of-care recommendations is that women are often under-represented in HIV clinical research. A recent systematic review identified that fewer than 20% of participants in ART studies, fewer than 40% in vaccination studies and only 11.1% of those in HIV curative-strategy studies have been female. 46,47 By design, study inclusion and exclusion criteria often have a male bias, particularly criteria relating to conception planning and pregnancy, resulting in fewer women qualifying for trials in the first place. Moreover, the majority of PLWH in North America and Europe, where registration trials are conducted, are men, and thus, there is a lower possibility for women to be enrolled. Also, it is well known that women may have more complex social lives, including childcare and other care responsibilities, which may impact their ability to become involved in clinical trials. 48 These issues are exacerbated by the fact that women are more likely to be late presenters, and that there are typically more screening failures amongst women. [Authors’ personal observations] Encouragingly, this situation is changing with more women-only trials being conducted, and with registration trials now requiring higher proportions of women be enrolled in studies to meet country and European Regulatory Authority requirements on gender equity. 49,50

***Gender differences in antiretroviral response***

Clinical studies in HIV have rarely focused solely on outcomes in women, with data on gender analysis often sparse and the subject of controversy. 17,22,46,51-53 Thus, it must be emphasised that treatment-outcome studies should, by design, report on gender-specific differences in virological responses and tolerability.

Studies suggest that there are gender inequalities in response to combination ART. A meta-analysis of clinical studies, assessing ART over a period of at least 48 weeks between 2000 and 2008, found several significant gender-related differences favouring better efficacy in men than in women. 54 The Swiss HIV Cohort study reported on outcomes in 3925 patients, of whom 1941 were women, with access to combination ART over a 14-year period (1998–2011). 22 Prior to starting ART, women in this cohort study were younger and had higher CD4 cell counts and lower viral load levels than men. One year following ART initiation, women were significantly less likely to achieve virological suppression than men (75.2% vs 78.1% p=0.029). This gender disparity in virological response rates persisted at 2 years, with 77.5% of women vs 81.1% of men (p=0.008) showing an undetectable viral load. In this cohort, women were also more likely to switch or discontinue treatment during the first year of ART; treatment discontinuations were only partly driven by pregnancy. The authors considered that gender inequalities in the response to ART were mainly explained by the different socioeconomic characteristics prevalent in the women in this cohort compared with the men. 22 Interestingly, by 5 years, the difference was no longer significant (81.3% of women vs 80.5% of men with undetectable viral load), suggesting that women eventually catch up with men in their response to ART. The determinants of the change in response rate over time deserve further analysis.

Data from the UK-based ASTRA study (Antiretrovirala, Sexual Transmission Risk and Attitudes study) again suggest that socioeconomic factors play a role in the observed gender differences in virological responses to ART. 55 Through a survey of participants at eight UK clinics, who had been receiving ART for at least 6 months, the ASTRA study found that women were less likely to have enough money for basic needs than men – one of several socioeconomic factors that was linked with women having a greater likelihood of having detectable viral load and experiencing viral load rebound after suppression than their male counterparts. Depression was noted as a significant determinant of reduced virological responses, regardless of gender.

In the ACTG A5257 study, a randomised trial of first-line ART regimens, the probability of virological failure by 96 weeks was significantly higher in women than in men (16% vs 11%) and the difference was again explained by ethnicity and sociodemographics. 56

There is also evidence that reduced virological responses amongst women translate into less favourable clinical outcomes. A Veterans Affairs retrospective cohort study reported on gender differences in overall burden of disease amongst PLWH after 1 year on ART. Although ART treatment improved disease burden in both genders, WLWH had significantly less improvement in overall disease burden than did men living with HIV, as measured by the Veterans Aging Cohort Study Index of HIV and non-HIV biomarkers predictive of morbidity and mortality. 57

***Women and ART adherence – implications for treatment initiation, maintenance and switching strategies***

Women are typically more reluctant to commence treatment and may demonstrate lower adherence rates to ART than their male counterparts. 58 Further, women are more likely to stop or switch their ART regimen in the first year on treatment, for reasons that are not wholly accounted for or driven by pregnancies. 22 Women’s approach to medical conditions differs from men; they face very different emotional challenges upon diagnosis. 17

One important issue relates to the impact of mental health on care outcomes. WLWH experience a disproportionate burden of mental health issues. A global survey comprising respondents from 94 countries assessed the prevalence of mental health problems before and after receiving a HIV diagnosis amongst women: one in five respondents reported problems before diagnosis, increasing by 3.5-fold post-diagnosis, with over 60% of respondents reporting depression, feelings of rejection, self blame, and a strong sense of isolation and anxiety, which might be expected to affect adherence. 59 Indeed data from the Women’s Interagency HIV Study, a US cohort of over 1000 women on ART in 2013–2014, showed a significant association between internalised stigma and suboptimal self-reported adherence amongst ethnic minority groups, and noted that depressive symptoms, loneliness, and low perceived social support mediate the association between internalised stigma and suboptimal adherence. 60

These findings clearly highlight the importance of obtaining adequate evaluations of mental health in newly diagnosed WLWH, addressing the influence of stigma on psychological wellbeing, and providing support around the time of initiation of ART and beyond.

***Gender-specific pharmacokinetics and drug–drug interactions***

Metabolic processes, and renal and hepatic function, differ between women and men. These basic gender differences influence drug handling in women and are modulated by factors such as ethnicity, pregnancy, endogenous hormones and use of exogenous sex hormones such as contraceptives and hormone-replacement therapy (HRT) across the woman’s lifetime. 17,51 Treatment guidelines describe potential ART-related drug–drug interactions – with a focus on interactions with antidepressants, antihypertensives, analgesics and corticosteroids, all of which can be regarded as not gender specific – and also include mention of drug–drug interactions between exogenous hormones that many WLWH may receive. 28 However, to date, there are very limited drug–drug interaction studies focused on WLWH. This is an important field of work as with ageing WLWH may require HRT and potentially additional treatments for comorbidities.

General gender considerations may also need to be applied to choice and selection of ART for women versus choices in men. For example, body weight and body mass index (BMI) in women affect drug disposition and handling. A study in a small cohort of WLWH found that in women with lower BMIs there was greater exposure to tenofovir disoproxil fumerate (TDF) than in women with higher BMIs, suggesting body weight and mass to be important considerations in drug selection amongst WLWH. 61 Another cross-sectional study looking at ART PKs in WLWH receiving their first combination ART, compared drug PKs with those for a reference HIV population of predominantly male patients. 51 It was found that the maximum serum concentration (Cmax) ratios for protease inhibitors (PIs) and non-nucleoside reverse transciptase inhibitors (NNRTIs) were significantly higher in WLWH than in the male population. This may explain the effect of gender on some specific toxicities that have been reported with antiretrovirals such as nevirapine. Women have also shown higher exposures than men to intracellular active drug concentrations such as the abacavir metabolite carbovir-trophosphate. 62

Available data on the effect of gender on ART PKs were summarised nicely in another scoping review. 17 There remains a need for more detailed analyses to clarify gender-related PK variability, drug interactions and ART-associated toxicities, in order to inform more appropriately tailored treatment choices.

***Antiretroviral drug toxicity and adverse events in WLWH***

Women appear to be at particular risk for certain ART-related drug toxicities and adverse events (AEs), and this may impact their cascade of care and treatment outcomes. The increased drug toxicities and AEs experienced by WLWH were previously summarised in another review.17 Long-term follow-up data from the FIRST trial of initial ART regimens (PI, NNRTI or PI + NNRTI-based combinations) suggest that WLWH have a more than twofold higher risk of treatment-related anaemia than do men living with HIV (HR=2.34, 95% confidence interval [CI]: 1.09 to 4.99). 63 A retrospective cohort study in over 630 PLWH found that women were more likely to stop ART due to AEs than men, the gender difference being apparent across all types of AEs (Figure 3). 64 Such reports highlight that women may be less able than men to tolerate certain antiretrovirals. Also, in general, women are at high risk of discontinuing ART because of AEs, as reported by cohort studies. 65 Gender-related effects have been reported for dolutegravir, with increased rates of drug discontinuation recently observed in a large retrospective cohort study, where women and older patients were more likely to discontinue dolutegravir secondary to all AEs and more specifically to neuropsychiatric AEs. 66 However, this was not seen in prospective phase III clinical trials, where overall rates of central nervous system (CNS) side effects were low. 67

It should be noted that the available data on drug toxicity refer largely to older ART regimens. Whether there are substantial differences between the genders in tolerability of newer antiretroviral agents remains to be explored in detail, although some reassuring data have started to emerge (see section on Women-only antiretroviral clinical trials).

## Women-only antiretroviral clinical trials

Few female-specific randomised clinical trials have been successfully completed, with the exception of the recently reported Women AntiretroViral Efficacy and Safety Study (WAVES) and Virus (HIV)-1 Infected Antiretroviral Therapy (ART) Naïve Women (ARIA) studies (Table 3). 49,50,68 These studies provide data on outcomes in contemporary women-only cohorts and are worth fully highlighting in this review.

The WAVES study is an international, double-blind, controlled study in treatment-naïve WLWH randomly assigned to receive one of two standard-of-care regimens: an integrase-inhibitor (INI) regimen (elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate [EVG/COBI/FTC/TDF]) or a boosted PI-based regimen – atazanavir/ritonavir/emtricitabine/tenofovir disoproxil fumarate (ATV/RTV/FTC/TDF). 49,68

The primary endpoint of WAVES was virological suppression at Week 48. Women in the INI-arm were significantly more likely to achieve viral load undetectability than those in the PI-arm (87% vs 81%; p=0.03) (Figure 4; Table 3). The INI regimen was shown to be more effective regardless of baseline CD4 cell count and viral load. No women developed genotypic drug resistance in the INI group vs 1% in the comparator group. The rate of discontinuations due to AEs was higher in the PI group (n=19) than in the INI group (n=5). WAVES was the first randomised control trial to be completed exclusively in women, and comprised a geographically and ethnically diverse cohort. Its findings, that the INI regimen was superior to the PI regimen, differ from some previous clinical trials performed in mostly male populations, where the outcome was regimen non-inferiority. In an open-label extension (OLE) to WAVES, virologically suppressed women could roll over from ATV/RTV/FTC/TDF to EVG/COBI/FTC/TAF or continue on the PI-based regimen. Women switching to EVG/COBI/FTC/TAF maintained high rates of virological suppression (94%) through to Week 48 of the OLE, and it was also found that treatment with EVG/COBI/FTC/TAF, compared with ATV/RTV/FTC/TDF, was associated with significant improvements in spine bone mineral density (BMD) (p<0.001) and tubular proteinuria (p<0.001) (Table 3). 68

Data have also been reported for the ARIA study, an international, open-label, study in treatment-naïve WLWH. 50 ARIA compared an INI-based regimen of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) with a boosted PI-based regimen of ATV/RTV plus TDF/FTC, with 48-week virological suppression as its primary outcome. The INI regimen was again statistically superior to the PI-based treatment, with 82% vs 71% of women achieving virological suppression (p=0.005) (Figure 5; Table 3), and with similar results according to predefined stratified groups, including baseline CD4 count <350 cell/mm3 and viral load >100,000 copies/mL. The INI group demonstrated a favourable safety profile, with fewer drug-related AEs and AEs leading to discontinuations than in the PI-based treatment group (4% vs 7%).

These are landmark studies for the management of HIV in women, not only for taking an all-women focus, but also for providing evidence to inform the choice of initial therapy for WLWH. Results indicate that INI-based regimens offer superior efficacy to PI-based regimens in ART-naïve WLWH. Crucially, the studies also contribute to the field by demonstrating that it is feasible to enrol and retain women in ART trials and to study ART in ethnically, geographically and socially diverse groups of WLWH.

## Unmet clinical needs and research gaps

As highlighted in this review, there are a number of unmet needs, both in terms of offer and uptake of HIV testing and in terms of linkage to care after HIV testing, demonstrated by many WLWH that appear to be exacerbated by the impact of social and stigma issues. 13,15-17,32 More research is needed into what both prevents and what encourages females to accept HIV testing. In addition, there is a need to study and define, for different communities and different age groups of WLWH, better ways to ensure prompt linkage to HIV care.

Whilst it is accepted that, like men, women will benefit from early ART initiation, there remain limited data to inform ART selection and measures required to encourage adherence and maintain strong engagement with care. Women-only and women-focused trials are growing in number and increasingly seen as important in mapping understanding of optimal patient care. However, there are few studies, prospective or retrospective, looking at ART adherence, tolerability and toxicity, and the potentially unique set of drug interactions facing women over a lifetime on treatment. As well as ensuring that women-only and women-focused studies are supported and conducted, there is a need to look at age-related factors affecting ART choices and treatment success by studying younger and older cohorts of WLWH.

Further studies on the PK profile of ART agents and drug–drug interactions in women receiving ART are essential, especially when new drugs become available with very limited data on drug exposure in women. Whilst guidance has traditionally been provided in the context of contraceptive use, other areas require attention. This is the case with HRT, for example. In the general population, HRT has been found to significantly reduce menopausal symptoms and prevent postmenopausal osteoporosis, and HRT may also reduce mortality and cardiovascular morbidity in menopausal women if started close to the time of ovarian failure. 69-80 How this evidence translates into the management of perimenopausal and postmenopausal WLWH, including consideration of any potential for drug–drug interactions, will be essential to determine.

As women age their bone health changes: BMD decreases, predisposing towards osteoporotic fracture risk. Vitamin D requirements change with age, but do so differently in darker-skinned compared with lighter-skinned women: again what might this mean for WLWH?

Some insights are emerging from the START study 81 and the gender subanalyses of other studies in treatment-naïve and switch patients. In the START study, of the 27% of women enrolled, 12.7% were postmenopausal. The WHO Fracture Risk Algorithm (FRAX®) equations were used to relate femoral neck BMD T-scores to fracture risk for postmenopausal women, and it was found that postmenopausal women, as might be expected, had lower BMD than premenopausal women, with significant differences in the spine.

Whilst there are some insights suggesting that choice of ART backbone may affect markers of bone health such as BMD (Figure 6), 53 there are still a number of unanswered questions about how best to determine an individual patient’s risks. Should women be assessed for fracture risk using tools like the WHO FRAX risk tool at an earlier age? What do we know about the long-term impact of chronic ART on bone health in women?

Similarly, further study is needed on the concept of premature ageing amongst WLWH, including data on whether ART affects timing of the menopause. More research is needed on the optimal age to start HRT considering the potential impacts of HRT on bone health, which may be affected by some ARTs. Will WLWH need higher doses of HRT to maintain their bone density and what impact do ART therapies have on women’s renal health? Understanding the comorbidities that WLWH face throughout different periods of their lives and as they age, may help our understanding of the impact of drug therapies and so inform treatment practices and mitigate the potentially negative impacts of age-, disease- and treatment-related factors. Crucially, care of WLWH must also include screening, identification and management of cancers associated with HIV, including an improved understanding of screening needs around certain cancers such as anal carcinoma amongst human papilloma virus-positive women. 82

In addition to ageing considerations and the optimal management of older WLWH, there are other populations of women that need attention. For example, there is very little research presented on young WLWH, a population that is emerging as especially vulnerable to incident HIV infection across Europe. 10 Adolescent girls and young women are populations with unique needs when it comes to ensuring good retention in care and adherence to treatment. 83-86 Younger women engage less in care and have higher rate of treatment interruption once started on ART. 87 Understanding and working with young WLWH to encourage high rates of care engagement will be crucial. Adolescent women may have different approaches to HIV and treatment – facing different stigmas and challenges depending on the way they acquired HIV (vertically or later in life) and, accordingly, their regimen and treatment history. Understanding the drug–drug interactions of ART with contraceptive agents is essential for this population, 28 and is an area that could benefit from further investigation.

Lastly, conducting women-only studies and increasing enrolment of women into ART clinical trials are essential. There is a need to understand why clinical trials attract and recruit low numbers of WLWH. Do investigators and protocols put up unnecessary barriers? Are the benefits of clinical trial enrolment not being well conveyed to WLWH? Do women fail trial recruitment screening and if so why? Is pregnancy or the prospect of pregnancy a stumbling block to female recruitment? Could committing to contraception in trials be a barrier to women who would prefer to see the achievement of undetectable viral load as an opportunity to feel ‘well-enough’ to conceive or to conceive ‘more safely’? How can we take better account of clinical, psychological and social needs of WLWH to facilitate greater inclusion in studies?

# Summary and Conclusions

This review of the unmet needs of WLWH across the cascade of HIV care suggests that there are still failings in the screening and identification of HIV in women. Despite some advances, women are still under-represented in ART clinical trials and there remains a substantial lack of analyses of outcomes by gender. More data are required on both younger and older WLWH, especially when it comes to understanding drug adherence, toxicities and AEs, and factors that impact on women’s approaches to care and treatment. Furthermore, we need to have a better understanding of the gender-specific factors affecting pharmacological drug handling, and its influence on drug efficacy and safety. Ageing, menopause and the long-term effects of comorbidities for WLWH require further consideration and studies that offer insights on how they affect women across the cascade of HIV care are essential to help inform individualised treatment planning. WLWH need management tailored to their age and lifestyle with choices made, refined and adapted according to reproductive intent, ageing and long-term health.

Reflecting these needs, the Women Against Viruses in Europe (WAVE) is a new working group and initiative by the European AIDS Clinical Society (<http://www.eacsociety.org/wave/about-wave/wave.html>), which aims to promote the welfare of WLWH in Europe, supporting equality of prevention efforts, access to care, excellence in standards of care and seeks to deliver and support WLWH through targeted education programmes. Such initiatives, plus more women-focused research may see some of the current unmet needs and gaps addressed to support the care and wellbeing of WLWH.

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