What's new for antiretroviral treatment in women with HIV

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Abstract

Currently, women represent 52% of persons infected with HIV worldwide and 23% of those in the United States. Combination antiretroviral therapy (cART) has resulted in remarkable reductions in HIV-associated morbidity and mortality, and has dramatically improved life expectancy. Treatment guidelines do not differ for HIV-infected men and non-pregnant women. However, clinical trials of antiretroviral agents have limited female enrolment, and results from these predominantly male studies are extrapolated to the female population. Furthermore, many of these studies do not report gender subgroup analyses, and those that do are underpowered to detect differences between men and women, limiting the ability to assess if results are equally applicable to both sexes. Women may have differential responses to and adverse events from cART. A limited number of female-only clinical trials have demonstrated that female recruitment and retention in these studies is feasible. Therefore, urgent attention is required to improve the body of knowledge regarding clinical efficacy, safety and tolerability of cART in women. In particular, women living with HIV are faced with various sexual and reproductive health concerns that may influence choice of cART. These include potential interactions with hormonal contraception, safety in pregnancy, and the impact of the transition through menopause and development of age-related comorbidities. Finally, the ongoing advances in biomedical HIV prevention, particularly pre-exposure prophylaxis (PrEP), provide an enormous opportunity to enhance HIV prevention in high-risk women, in efforts to further reduce global burden of the pandemic.

Keywords: HIV, women, antiretroviral therapy, PrEP

Introduction

The epidemiology of the human immunodeficiency virus (HIV) pandemic has evolved over the years. Women now represent 52% of the 36.9 million people worldwide living with HIV [1,2], and 23% of infected individuals in the United States (USA) [3]. Women face many unique challenges with respect to HIV, including greater biological predisposition to HIV acquisition, increased susceptibility to violence, difficulties in advocating for protected sexual intercourse, unequal educational and socioeconomic opportunities, and greater primary-care responsibilities that can impact HIV knowledge and impede access to and retention in care and utilisation of therapy [1,3].

Combination antiretroviral therapy (cART) has dramatically improved morbidity and mortality for people living with HIV [4,5]. Women are underrepresented in antiretroviral (ARV) clinical trials, and treatment recommendations are extrapolated from studies in predominantly male populations. However, sex differences in ARV pharmacokinetics may influence drug efficacy and predisposition to certain adverse events (AEs) in women compared to men [6,7]. Furthermore, the pharmacologic management of HIV requires consideration of key sexual and reproductive health concerns, including drug-drug interactions with hormonal contraception (HC), use of ARVs to prevent mother-to-child transmission, management of HIV-infected women in the context of age-associated comorbidities, and menopause, and the benefits and risks of novel biomedical HIV-prevention strategies, such as pre-exposure prophylaxis (PrEP).

Women in pivotal cART clinical trials

As newer ARVs are developed and further clinical trials conducted, management recommendations for treatment-naïve, HIV-infected adults continue to evolve. Regional HIV guidelines vary in their preferred first-line regimens (Table 1) [6,8–11]; however, emerging evidence and guideline revisions have resulted in a transition towards simplified regimens with proven efficacy and increasingly favourable side-effect profiles. Preferred treatment of HIV-infected adults includes a dual nucleoside reverse-transcriptase inhibitor (NRTI) backbone, in combination with an integrase strand transfer inhibitor (INSTI), protease inhibitor (PI) (boosted with cobicistat or ritonavir), or non-nucleoside reverse-transcriptase inhibitor (NNRTI) [6,8]. In the last year, the USA Department of Health and Human Services (DHHS) [6] and the European AIDS Clinical Society (EACS) [8] have revised their recommended cART regimens to favour INSTI-based therapy, and have largely moved away from NNRTI-based regimens due to adverse events, particularly central nervous system (CNS) toxicities. The World Health Organization (WHO) continues to recommend NNRTI-based therapy, particularly in resource-limited settings [10].

The indications for treatment initiation and the recommended regimens for HIV-infected women are the same as for other infected adults, with additional caveats that practitioners consider potential drug interactions with hormonal contraception, and be aware of well-established gender differences in toxicity of certain ARVs [6]. This is exemplified by the well-recognised risk of nevirapine-associated hepatotoxicity in women with CD4 counts >250 cells/mm^3 [6,12]. Treatment recommendations are based on pivotal cART clinical trials that have limited female enrolment (Table 2) [13–35], and have traditionally excluded those who are pregnant or breastfeeding. Furthermore, these clinical trials do not universally report subgroup analyses by sex, and those that do are underpowered to detect significant differences due to the limited number of female participants [36]. When gender-based subgroup analyses are reported, they are typically for the primary efficacy endpoint only, and do not address differences in adverse events. To date, there are only two randomised, all-women, cART clinical trials. The WAVES study [26] investigated efficacy and safety of elvitegravir (EVG), while the ongoing ARIA trial is investigating use of dolutegravir (DTG) [*ClinicalTrials.gov* NCT01910402]. Separate guidelines have been developed for the use of cART in women who are pregnant or planning to become pregnant, as recommended

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Table 1. Regional guidelines for treatment of antiretroviral-naïve HIV-1-infected adults

Guideline	DHHS [6]	EACS [8]	IAS-USA [9]	WHO [10,11]
Last updated	January 2016	October 2015	July 2014	2013 [Timing recommendation updated September 2015]
Timing of initiation	ART is recommended for ALL HIV-infected individuals **regardless of CD4 cell count** and including those with early HIV infection (AI)*	ART is strongly recommended for symptomatic and asymptomatic patients with HIV, irrespective of CD4 cell count, with the possible exception of elite controllers with high and stable CD4 cell count	ART is recommended for the treatment of HIV infection and for the prevention of HIV transmission ART is recommended **regardless of CD4 cell count**; the strength of this recommendation increases as CD4 cell count decreases and with presence of other indications* • CD4 ≤500/μL (AIa) • CD4 >500/μL (BIII) • Pregnancy (AIa) • Chronic HBV (AIIa) • HIVAN (AIIa)	ART is recommended in all adults with HIV infection at any CD4 cell count As a priority, ART should be initiated in adults with severe or advanced HIV clinical stage (WHO clinical stage 3 or 4) and individuals with CD4 ≤350 cells/mm^3 ART should be initiated in all pregnant and breastfeeding women with HIV at any CD4 cell count and continued lifelong
Preferred regimens				
INSTI-based	ABC/3TC/DTG[a] TDF/FTC/DTG TDF/FTC/EVG/c[b] TAF/FTC/EVG/c[c] TDF/FTC/RAL	ABC/3TC/DTG TDF/FTC/DTG TDF/FTC/EVG/c[b] TDF/FTC/RAL	ABC/3TC/DTG[a] TDF/FTC/DTG TDF/FTC/EVG/c TDF/FTC/RAL	
PI-based	TDF/FTC/DRV/r	TDF/FTC/DRV/r	TDF/FTC/DRV/r TDF/FTC/ATV/r ABC/3TC/ATV/r[a]	
NNRTI-based		TDF/FTC/RPV[d,e]	TDF/FTC/RPV[d,e] TDF/FTC/EFV ABC/3TC/EFV[a]	ZDV/3TC/EFV TDF/FTC (or 3TC)/EFV ZDV/3TC/NVP TDF/FTC (or 3TC)/EFV

DHHS: Department of Health and Human Services; EACS: European AIDS Clinical Society; IAS: International Antiviral Society USA; WHO: World Health Organization; ART: antiretroviral therapy; INSTI: integrase strand transfer inhibitor; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; ABC: abacavir; 3TC: lamivudine; DTG: dolutegravir; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; EVG: elvitegravir; c: cobicistat; TAF: tenofovir alafenamide; RAL: raltegravir; DRV: darunavir; r: ritonavir; RPV: rilpivirine; HBV: hepatitis B virus; HIVAN: HIV-associated nephropathy; EFV: efavirenz; ZDV: zidovudine; NVP: nevirapine.

* Levels of evidence: AI: strong recommendation for statement, one or more randomised trials with clinical outcomes and/or validated laboratory results [6]; AIa: strong support, evidence from one or more randomised controlled trials (RCTs) published in the peer-reviewed literature; AIIa: strong support, evidence from non-RCTs, cohort, or case-control studies published in the peer-reviewed literature; BIII: moderate support, recommendation based on the panel's analysis of the accumulated available evidence [9].

[a] For patients who are HLA-B*5701 negative.

[b] For patients with pre-treatment creatinine clearance (CrCl) ≥70 mL/min.

[c] For patients with pre-treatment CrCl ≥30 mL/min.

[d] To be taken with food: minimum 390 Kcal required; do not co-administer with proton-pump inhibitors; use with caution in patients on other acid-suppressing medications.

[e] Not for patients with pre-treatment viral load ≥100,000 copies/mL or CD4 ≤200 cells/μL.

regimens in this population favour those with established safety and efficacy in pregnancy [37].

Nucleoside reverse-transcriptase inhibitor backbone

Abacavir/lamivudine *vs* tenofovir/emtricitabine

Efficacy

Based on established efficacy and safety, the two recommended NRTI backbones are abacavir/lamivudine (ABC/3TC) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) [6,8]. Backbone selection depends on several factors, including viral set point, co-morbidities (particularly hepatitis B co-infection), potential toxicities, and co-formulation with a third agent into a single-tablet regimen (STR), which can reduce pill burden and improve adherence to therapy [6,38,39].

The clinical efficacy of these two backbones was compared in three clinical trials: HEAT, ASSERT and ACTG 5202 [13–17]. The proportion of women enrolled in each of these studies was <20% (Table 2). The HEAT trial compared ABC/3TC to TDF/FTC, both in combination with lopinavir/ritonavir (LPV/r), and found no difference between the two arms in virological suppression or safety [13]. No gender subgroup analysis was reported [13]. In the ASSERT trial, where the third agent was efavirenz (EFV), the primary endpoint was change in baseline renal function; however, secondary endpoint analysis demonstrated a higher likelihood of achieving virological suppression in participants receiving TDF/FTC; again no gender subgroup analysis was reported [14].

In AGTG 5202, the two backbones were compared on a randomised third agent of either EFV or ritonavir-boosted-atazanavir (ATV/r) (Table 2) [15]. The study was terminated prematurely by the data safety monitoring board (DSMB) due to excess virological failures with ABC/3TC when baseline viral load (VL) was ≥100, 000 copies/mL. Of the 797 patients with VL≥100, 000 copies/mL, 15% were women [15]. A subgroup analysis demonstrated a significant interaction by sex: men were three times more likely to experience virological failure (VF) with ABC/3TC, but for women, there was no difference in VF between the two backbones. This conclusion must be interpreted with caution, as the limited number of women resulted in a wide confidence interval [15]. Safety endpoints were not reported by sex. In the 96-week analysis of all enrolled

Table 2. Inclusion of women in pivotal antiretroviral clinical trials

Trial	Design	Investigational drug(s)	Total enrolment	Proportion of women	Overall findings	Sex-based analysis	Results of subgroup analysis
HEAT [13]	Double-blind, placebo-matched, randomised, non-inferiority trial Third agent: LPV/r	ABC/3TC *vs* TDF/FTC	694	16% in ABC/3TC arm 20% in TDF/FTC arm	No difference in proportion with virological suppression at week 48 No difference in safety endpoints	No	
ASSERT [14]	Randomised, open-label trial Third agent: EFV	ABC/3TC *vs* TDF/FTC	385	17% in ABC/3TC arm 20% in TDF/FTC arm	No difference in change from baseline renal function or drug-related AEs Greater proportion achieved virological suppression in TDF/FTC arms in those with VL <100,000 and those with VL ≥100,000	No	
ACTG A5202 [15]	Phase III, partially blind, randomised clinical trial Four study arms: ABC/3TC + EFV ABC/3TC + ATV/r TDF/FTC + EFV TDF/FTC + ATV/r	ABC/3TC *vs* TDF/FTC	797 with baseline VL ≥100, 000	15% in stratum with viral load ≥100, 000	In high VL stratum, shorter time to virological failure with ABC/3TC (HR 2.33)	Yes	Higher virological failure with ABC/3TC in men (HR 3.00, 95% CI 1.74–5.17) **but not women** (HR 0.85, 95% CI 0.30–2.89)
ACTG A5202 [16]		ABC/3TC *vs* TDF/FTC	1857 (total population)	17%	No difference in time to virological failure between two NRTI backbones at 96 weeks	No	
ACTG A5202 [17]		ATV/r *vs* EFV	1857	17%		Yes	For women, higher risk of virological failure with ATV/r *vs* EFV in both ABC/3TC backbone (HR 2.55, 95% CI 1.20–5.41) and TDF/FTC backbone (HR 2.16, 95% CI 0.97–4.80) With ATV/r, higher risk of virological failure for women *vs* men (HR 1.72, 95% CI 0.99–2.99)
SINGLE [18,19]	Phase III, double-blind, placebo-matched, non-inferiority RCT Two study arms: ABC/3TC/DTG *vs* TDF/FTC/EFV	DTG	833	16%	DTG-regimen both inferior and superior to EFV-regimen in achievement of virological suppression at week 48 • 88% *vs* 81% in ITT analysis • 90% *vs* 81% in per-protocol analysis, showing superiority	Yes	In women, 57/67 (85%) achieved virological suppression with DTG *vs* 47/63 (75%) with EFV (non-significant trend appears to favour DTG arm)
SPRING-2 [19,20]	Phase III, double-blind RCT DTG *vs* RAL; NRTI backbone at investigator's discretion	DTG	822	15% in DTG group 14% in RAL group	DTG non-inferior to RAL in achievement of virological suppression	Yes	In women, 162/186 (87%) achieved virological suppression with DTG *vs* 18/291 (83%) with RAL (non-significant trend appears to favour DTG group)
FLAMINGO [19,21]	Open-label RCT DTG *vs* DRV/r NRTI backbone at investigator's discretion	DTG	484	15%	DTG both non-inferior and superior to DRV/r in achievement of virological suppression	Yes	In women, 26/31 (84%) achieved virological suppression in DTG group *vs* 30/41 (73%) in DRV/r group (non-significant trend appears to favour DTG group)
GS-US-236-0102 [22,23]	Phase III, double-blind, placebo-matched RCT Study arms: TDF/FTC/EVG/c *vs* TDF/FTC/EFV	EVG/c	700	11%	No difference in achievement of virological suppression between EVG/c (87.6%) and EFV (84.1%) at week 48 Higher mean increase in CD4 cell count with EVG/c *vs* EFV At week 144, virological suppression was 80.2% with EVG/c and 75.3% with EFV; lower drug discontinuation with EVG/c	Yes	No difference between men and women in proportion achieving virological suppression at week 48 At week 144, 78% of women in EFV and EVG/c groups had virological suppression; for men, 80.2% suppressed with EVG/c *vs* 75.3% with EFV (appears to favour EVG/c)

Table 2. Continued

Trial	Design	Investigational drug(s)	Total enrolment	Proportion of women	Overall findings	Sex-based analysis	Results of subgroup analysis
GS-236-0103 [24,25]	Phase III, double-blind, placebo-matched, non-inferiority RCT Study arms: TDF/FTC/EVG/c *vs* TDF/FTC/ATV/r	EVG/c	708	8% in EVG/c group 11% in ATV/r group	No difference in achievement of virological suppression between EVG/c (89.5%) and ATV/r (86.8%) at week 48 At week 144, no difference in rates of virological suppression between two groups	Yes	No difference between men and women in proportion achieving virological suppression at week 48 At week 144, 62% of women in EFV group and 52% of women in EVG/c had virological suppression; wide CI but trend to favouring ATV/r
WAVES [26]	Phase III, double-blind RCT Study arms: TDF/FTC/EVG/c *vs* TDF/FTC/ATV/r	EVG/c	575	100%	At week 48, 87.2% of women in EVG/c group and 80.8% of women in ATV/r group had virological suppression (difference 6.5%; 95% CI 0.4–12.6%) confirming non-inferiority Similar mean increase in CD4 cell count (221 cells/mm^3 with EVG/c and 212 cells/mm^3 with ATVr/)	N/A	
STARTMRK [27,28]	Phase III, double-blind, non-inferiority RCT Study arms: TDF/FTC/RAL *vs* TDF/FTC/EFV	RAL	563	19%	At 48 weeks, virological suppression achieved in 86.1% in RAL group *vs* 81.9% in EFV group, confirming non-inferiority	No (48 weeks) Yes (5 years)	At 5 years (*n*=43 women), 90% of women in RAL group and 85% of women in EFV group had virological suppression (trend to favouring RAL) Trend to higher mean change in CD4 for women on RAL *vs* EFV (383 cells/mm^3 *vs* 327 cells/mm^3)
ACTG 5257 [29]	Phase III, open-label RCT NRTI backbone: TDF/FTC	RAL *vs* ATV/r *vs* DRV/r	1809	24%	No difference in proportion of patients with virological failure at 96 weeks between the three regimens	Yes	In women, no difference in rate of virological failure between three regimens at 96 weeks (23.8% for ATV/r, 23.8% for DRV/r and 24.5% for RAL
ARTEMIS [30,31]	Phase III, open-label RCT Study arms: TDF/FTC/DRV/r *vs* TDF/FTC/LPV/r	DRV/r	689	30%	Virological suppression achieved by 84% of those on DRV/r *vs* 78% of those on LPV/r, confirming non-inferiority of DRV/r At week 192, DRV/r was both non-inferior and superior in clinical efficacy compared to LPV/r	No (48 weeks) Yes (192 weeks)	At week 192, 71.2% of women in DRV/r group and 56.2% of women in LPV/r group had virological suppression, favours DRV/r
Pooled ECHO and THRIVE [32–34]	Phase III, double-blind RCTs ECHO: RPV *vs* EFV (both with TDF/FTC) THRIVE: RPV *vs* EFV (with ABC/3TC, TDF/FTC or ZDV/3TC)	RPV	1368	24%	RPV non-inferior to EFV for virological suppression at 48 weeks; in ECHO, higher risk of virological failure with RPV when baseline VL≥100,000 copies/mL	Yes	At week 48, no differences between men and women with virological suppression with either RPV (85% men and 83% women suppressed) or EFV (82% men and 83% women suppressed)
STaR [35]	Phase IIIb, open-label RCT comparing two STRs TDF/FTC/EFV *vs* TDF/FTC/RPV	RPV	786	7%	RPV non-inferior to EFV for virological suppression and mean change in CD4 cell count *Post hoc* analysis: trend to reduced response for RPV when baseline VL >500,000 copies/mL	No	

ABC: abacavir; 3TC: lamivudine; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; LPV/r: ritonavir-boosted-lopinavir; EFV: efavirenz; AE: adverse event; VL: viral load; ATV/r: ritonavir-boosted-atazanavir; HR: hazard ratio; CI: confidence interval; *vs*: versus; DTG: dolutegravir; ITT: intention-to-treat; NRTI: nucleoside reverse transcriptase inhibitor; RAL: raltegravir; DRV/r: ritonavir-boosted-darunavir; EVG/c: cobicistat-boosted-elvitegravir; RPV: rilpivirine; BMD: bone mineral density; ZDV: zidovudine; STR: single-tablet regimen.

participants (17% women), there was no difference in time to virological failure between the two backbones [16].

NRTI toxicity considerations for women

Abacavir is associated with potentially fatal hypersensitivity reactions in individuals carrying the HLA-B*5701 allele, and should be avoided in those who are positive on pre-treatment genetic testing [6,40]. This genetic marker does not differ in prevalence by gender [40,41]. The literature also suggests a potential association between ABC and increased cardiovascular events [42,43], but this association has not been consistently demonstrated [44,45]. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort, increased cardiovascular risk was evident in both men and women [42]. The VA study [46] demonstrated an increase in cardiovascular disease (CVD) in HIV-infected women relative to HIV-negative controls. Women have some hormonal protection from CVD until they transition through menopause; however, menopause is reported to occur earlier in women with HIV compared to the general population [47–49], which may further increase susceptibility to cardiovascular events.

TDF is associated with renal dysfunction and osteoporosis, and should be used with caution in patients who have established, or are at high risk, of renal or bone disease [6]. Increased loss of bone mineral density (BMD) has been observed with the use of TDF, relative to abacavir, in men and women [14,15]; while this complication has not modified treatment recommendations for post-menopausal, HIV-infected women, the menopausal transition may be a period of particular vulnerability to the bone toxicity associated with TDF. Specific bone disease management guidelines in HIV suggest that in addition to aggressive osteoporosis management, clinicians may elect to avoid TDF-based regimens in those with high fracture risk [50].

The tenofovir pro-drug, tenofovir alafenamide (TAF) is associated with less BMD loss with cART initiation than TDF [51]. Furthermore, switching from TDF to TAF has been shown to significantly increase BMD in two large studies of predominantly men who have sex with men (MSM) (10% women, mean age 40 years) [52,53], and in a third study of participants with impaired renal function, in which there was a higher proportion of older HIV-positive individuals (20% women, mean age 58 years) [54]. Whether the same increase in BMD, and associated decreased risk of fracture, will occur in peri- and post-menopausal women is unknown. Although there are no recommendations for cART modification in ageing women with HIV, the peri-menopausal period is an important time during which the choice of NRTI backbone, in consideration with these cardiovascular, renal and osteoporotic risks, should be reassessed.

Third antiretroviral agent

Integrase strand transfer inhibitors

Dolutegravir

Dolutegravir (DTG) is an INSTI with demonstrated efficacy, minimal side effects, and a high genetic barrier to resistance; it is the recommended third agent in two preferred cART-regimens [6,8,9]. DTG has a prolonged half-life, which supports once-daily dosing and regimen simplification [18]. It can be co-formulated with ABC/3TC into a single-tablet regimen (e.g. Triumeq), or combined with TDF/FTC [6,8,9].

The inclusion of dolutegravir-based regimens as first-line cART is based on three clinical trials (Table 2). The proportion of women in each of these trials was ≤16%; pregnant and breastfeeding women were excluded [18–21]. Subgroup analyses by gender were reported in each of these studies, demonstrating virological suppression rates of 84–85% in men and women [19]. In SINGLE [18] the ABC/3TC/DTG-regimen met criteria for non-inferiority and superiority relative to TDF/FTC/EFV; these results were in large part due to the higher tolerability of DTG compared to EFV, and higher discontinuation rate in the EFV arm. In women, virological suppression was achieved in 85% of participants in the DTG-group, compared to 75% in the EFV-group; the point-estimate favoured ABC/3TC/DTG; however, this was a non-significant trend with a wide confidence interval [18,19]. In SPRING-2 [20], DTG was non-inferior to raltegravir (RAL), in combination with an investigator-selected NRTI backbone. Virological suppression rates in women were 87% for DTG and 83% for RAL, a non-significant finding that appeared to favour DTG [19,20]. In the FLAMINGO study [21], DTG was non-inferior and superior to ritonavir-boosted darunavir (DRV/r). For female participants, subgroup analysis once again favoured DTG non-significantly, with 84% of women on DTG achieving virological suppression, compared to 73% with DRV/r [19,21]. Discontinuation rates due to AEs in these studies were low, and not reported by gender.

Given the limited interpretation of subgroup analyses due to low female enrolment in these trials, the results of ARIA, an *all-women* RCT comparing ABC/3TC/DTG to TDF/FTC/ATV/r, will be instrumental in further informing the efficacy and safety of DTG in treatment-naïve, HIV-infected women.

Elvitegravir

Elvitegravir (EVG) is an INSTI that requires pharmacokinetic boosting with the cytochrome (CYP) P450 3A4 inhibitor, cobicistat (denoted as /c). EVG is a recommended first-line agent for treatment of HIV-1 infection in combination with cobicistat and TDF/FTC [6,8,9]. This regimen is available as a co-formulated STR (Stribild). EVG/c is also licensed in the USA and Canada as a first-line regimen in combination with TAF/FTC (Genvoya) [6,55].

The efficacy of EVG in treatment-naïve subjects was demonstrated in two clinical trials; women represented ≤11% of the study populations [22,24] (Table 2). These studies demonstrated non-inferiority of EVG/c relative to ATV/r and EFV. Sex-based subgroup analyses showing no differences were reported for the primary efficacy endpoint only, but not for differences in AEs. For men, the point estimates for proportion achieving virological suppression appeared to favour EVG/c (80.2%) over EFV (75.3%) at 144 weeks; this trend was not observed for women [23]. Virological suppression occurred for 52% of women on EVG/c compared to 62% on ATV/r after 144 weeks of therapy; although this appeared to favour ATV/r, the wide confidence interval and small number of female participants limits interpretation of this finding [25].

The WAVES study [26], a Phase III, double-blind, international RCT, is the first, *all-women* clinical trial, and compares treatment-naïve, HIV-infected women initiating EVG/c or ATV/r, both in combination with TDF/FTC. The study enrolled 575 women (mean age 35 years) and preliminary results were presented at the International AIDS Society (IAS) 2015 Conference. The primary efficacy endpoint was proportion with virological suppression (VL <50 copies/mL) at week 48; this was achieved in 87.2% of women on EVG/c and 80.8% of women on ATV/r, indicating superiority of EVG/c. There were similar mean increases in CD4 cell count, and no differences in development of renal dysfunction, renal adverse events, or changes in BMD [26]. Importantly, women who became pregnant during the study were allowed to continue the study drug (*n*=24 pregnancies; *n*=13 who continued study drug). Again the differences were largely driven by tolerability, with more women in the ATV/r group developing jaundice, hyperbilirubinaemia or gastrointestinal AEs. While these study results appear to support

the use of EVG/c in women as a first-line regimen, it is important to see whether results are maintained with longer follow-up. This study has demonstrated that successful recruitment and retention of women in large ARV clinical trials is feasible; further clinical trials in women are encouraged to ensure that treatment guidelines apply equally to both genders.

Raltegravir

Raltegravir (RAL) was the first approved INSTI [6] and the first INSTI to be included as a first-line regimen for treatment-naïve, HIV-infected adults, in combination with TDF/FTC [6,8,9]. RAL is dosed twice daily and has a lower genetic barrier to resistance than DTG. While pregnant and breastfeeding women were excluded from the clinical trials establishing safety and efficacy of RAL, experience with this agent in pregnancy has accumulated [56], and RAL is also included as a preferred regimen for HIV-infected pregnant women [37].

The STARTMRK trial [27] demonstrated non-inferiority of RAL relative to EFV at 48 weeks. With prolonged follow up, the proportion of patients with virological suppression was 71% for RAL and 61.3% for EFV, demonstrating non-inferiority and superiority [28]. Of the 43 women who completed 5 years of follow-up, 90% on RAL maintained virological suppression, compared to 85% with EFV; this appeared to favour RAL, but statistical significance was not achieved [28]. Similarly, there was a non-significant trend towards higher mean increase in CD4 cell count for women on RAL compared to EFV (383 cells/mm^3 *vs* 327 cells/mm^3, respectively).

ACTG 5257 compared three regimens (ATV/r *vs* DRV/r *vs* RAL), each with TDF/FTC [29]. At 96 weeks, the proportion of individuals who experienced VF was similar between the three treatment arms (12.6% for ATV/r, 14.9% for DRV/r, and 9.0% for RAL). Women comprised 24% of the study population and a subgroup analysis was performed: the proportion of women who experienced virological failure was 23.8% for ATV/r, 23.8% for DRV/r and 24.5% for RAL, indicating no differences in clinical efficacy between the three regimens [29]. A study with a newer formulation of RAL, with once-daily dosing, has been completed and shows non-inferiority relative to the standard product. The results are only available as a press release and have not yet been presented; only 10% of participants were women [57].

Protease inhibitors

Darunavir (DRV) is the only PI included as a first-line regimen in updated guidelines from the USA and Europe (Table 1) [6,8]. DRV can be dosed once daily, and requires pharmacokinetic boosting with ritonavir (DRV/r) or cobicistat (DRV/c) [6].

Efficacy of DRV/r was established in the ARTEMIS trial [30], in which DRV/r was shown to be non-inferior to LPV/r in combination with TDF/FTC in ARV-naïve subjects; 30% of participants were women, but no subgroup analysis was reported at 48 weeks. In the 192-week results [31], DRV/r was non-inferior and superior to LPV/r with respect to virological suppression in all participants. In the subgroup analysis, clinical efficacy significantly favoured DRV/r over LPV/r in both men and women. Of the female participants, 71.2% maintained virological suppression on DRV/r [31].

Atazanavir (ATV) can be boosted pharmacokinetically with ritonavir (ATV/r) or cobicistat (ATV/c). Recent guidelines from the DHHS and EACS have modified recommendations for ATV, such that it is now an alternative, and not recommended, first-line antiretroviral [6,8]. This modification was based on findings from ACTG 5257, where although ATV/r was considered virologically equivalent to DRV/r and RAL, investigators observed a higher rate of drug discontinuation in the ATV/r arm due to AEs [29].

ACTG 5202 (described above) (Table 2) did not show gender differences in efficacy or tolerability of the two NRTI backbones; however, 96-week subgroup analysis showed that in the female participants, risk of VF was significantly higher with ATV/r compared to EFV, when combined with ABC/3TC (hazard ratio [HR] 2.55), with a trend to higher VF for ATV/r *vs* EFV when combined with TDF/FTC (HR 2.16) [17]. Women on ATV/r also had a higher risk of VF than men on ATV/r. Pharmacokinetic studies demonstrated slower ATV clearance and higher pre-dose ATV levels, indicating that VF was not due to sub-therapeutic drug concentrations [17]. Differences in risk of VF between ATV/r and EFV were not observed in males, and there were no noted differences in safety or tolerability between ATV/r and EFV in either men or women [17].

Although ATV/r is no longer a recommended first-line agent in adults, it continues to be recommended for treatment of pregnant, HIV-infected women due to extensive experience in pregnancy, and demonstrated efficacy and safety in this population [37].

Non-nucleoside reverse transcriptase inhibitors

Rilpivirine

Rilpivirine (RPV) is a first-line agent for HIV treatment in guidelines from the International Antiviral Society USA (IAS-USA) and Europe [8,9]; however, the 2016 DHHS guidelines classify RPV (with TDF/FTC) as an alternative regimen [6]. This is based on findings of reduced clinical efficacy in patients with high baseline viral loads ≥100,000 copies/mL and low CD4 cell counts ≤200 cells/mm^3 [6,8,32]. Additionally, RPV must be consumed with a high calorie meal (minimum 390 kcal), which may be challenging for many HIV-infected women. Rilpivirine is now also approved in a co-formulated STR with TAF in the USA (Odefsey) [58].

Efficacy of RPV was established in three large clinical trials (Table 2). In ECHO, RPV was non-inferior to EFV (with TDF/FTC) in achievement of virological suppression at 48 weeks; however, risk of virological failure was higher for RPV in the subgroup of patients with baseline VL ≥100,000 copies/mL and VL ≥500,000 copies/mL [32]. THRIVE also demonstrated non-inferiority of RPV to EFV (with ABC/3TC, TDF/FTC or zidovudine (ZDV)/3TC) [33]. Women accounted for 23% and 26% of participants in the RPV arms and 20% and 28% of participants in the EFV arms in ECHO and THRIVE respectively. A pooled gender analysis (total 1368 patients; 24% women), demonstrated no differences between men and women in achieving virological suppression at week 48: in the RPV group, 85% of men and 83% of women had VL <50 copies/mL, and in the EFV group, 82% of men and 83% of women had suppressed VL [34]. Nausea was more common in women, while men were more likely to experience diarrhoea (with EFV) and CNS toxicity (with RPV and EFV). The STaR trial [35] also demonstrated non-inferiority of RPV to EFV for virological suppression and mean change in CD4 cell count, with less drug discontinuation due to AEs with RPV. However, women represented only 7% of the total study population in this trial; no subgroup analysis by sex was performed [35].

Efavirenz

The clinical efficacy and safety of EFV (with TDF/FTC) has been established in multiple clinical trials over the years [15,16,32,33,59]. Although the IAS and WHO still recommend this agent as first-line therapy [9,10], many other guidelines [6,8] have switched EFV to the alternative category; this has occurred as several clinical trials have demonstrated superiority of other regimens when compared with EFV [18,27], mainly because of tolerability and toxicity, particularly CNS toxicity and increased risk of suicidality

Table 3. Drug–drug interactions between hormonal contraception and antiretroviral therapy [6,63]

Antiretroviral drug class	Specific antiretroviral	Interaction with hormonal contraception	Dose modification
NRTIs	N/A	N/A	None
PIs	ATV (unboosted)	Increased ethinyl oestradiol Increased norethindrone	COC should contain no more than 30 µg ethinyl oestradiol or recommend alternative contraception method; no data on COC with <25 µg ethinyl oestradiol or progestins other than norethindrone or norgestimate
	ATV/r	Reduced ethinyl oestradiol Increased norgestimate	COC should have minimum 35 µg ethinyl oestradiol
	ATV/c or DRV/c	Unknown interaction with COC	Recommend alternative contraception method or alternative ARV
	LPV/r	Reduced ethinyl oestradiol Reduced norethindrone Increased etornogestrel (subdermal implant) Increased transdermal ethinyl oestradiol but reduced transdermal norelgestromin	For COC: recommend alternative contraception method or alternative ARV For subdermal implant: no adjustment required For transdermal patch: no adjustment required
	Ritonavir-boosted PIs other than ATV/r or LPV/r	Reduced ethinyl oestradiol Reduced norethindrone Unknown interaction with etornogestrel implant Unknown interaction with transdermal patch	For COC: recommend alternative contraception method or alternative ARV For subdermal implant or transdermal patch: recommend alternative contraception method or alternative ARV
NNRTIs	EFV	No effect on ethinyl oestradiol Reduced levonorgestrel Reduced norelgestromin Reduced etornogestrel (subdermal implant)	For COC: use additional or alternative contraception For subdermal implant: use additional or alternative contraception
	NVP	Reduced ethinyl oestradiol Reduced norethindrone No effect on DMPA	For COC: use alternative or additional contraception For DMPA: no adjustment needed
	RPV and ETR	Increased ethinyl oestradiol No change to norethindrone	For COC: no adjustment needed
INSTIs	EVG/c	Reduced ethinyl oestradiol Increased norgestimate	Weigh risks and benefits of increased progestin; consider alternative contraception methods
	RAL and DTG	No change for ethinyl oestradiol or norgestimate	For COC: no adjustment needed

NRTIs: nucleoside reverse-transcriptase inhibitors; ATV: atazanavir; PIs: protease inhibitors; ATV/r: ritonavir-boosted atazanavir; COC: combined oral contraception; DRV/r: ritonavir-boosted-darunavir; ARV: antiretroviral; LPV/r: ritonavir-boosted-lopinavir; NNRTIs: non-nucleoside reverse-transcriptase inhibitors; EFV: efavirenz; NVP: nevirapine; DMPA: depo-medroxyprogesterone acetate; RPV: rilpivirine; ETR: etravirine; INSTIs: integrase strand transfer inhibitors; EVG/c: cobicistat-boosted elvitegravir; RAL: raltegravir; DTG: dolutegravir.

[60]. Over the years, clinical experience with EFV use in pregnancy has largely allayed concerns regarding teratogenicity [6,10,37,56]; while a potential association with neural tube defects cannot be definitively excluded [37], the evidence is inconsistent, and the main concern appears to be restricted to the first trimester. Therefore, EFV-based regimens are now recommended for pregnant women who present in the first trimester, after the period of potential teratogenicity has passed [10,37].

Sexual and reproductive health

Contraception

Elimination of HIV infection in children represents an ambitious, but attainable, global target [1]. In 2014, there were 220,000 new infections in children, representing a 58% reduction since 2000 [2]. Prevention of mother-to-child transmission requires a comprehensive strategy that begins with pre-conception care among HIV-infected women of reproductive age. Access to effective contraception to prevent unintended pregnancies, particularly in areas of high HIV prevalence, is a public health priority [6,61].

Hormonal contraception (HC) is available as both combined oestrogen/progestin and progestin-only formulations, can be delivered via oral, injectable, transdermal or implantable routes, and is highly effective in preventing pregnancy [62,63]. Concerns regarding use of HC in HIV-infected women have centred on two issues: whether HC affects prognosis of HIV infection among women on ART, and whether ART decreases effectiveness of HC. While some studies have shown that HC may adversely affect progression of HIV infection [64], many others have failed to replicate this finding [65,66] and a systematic review of 10 cohort studies indicated that HC was not associated with accelerated progression of HIV infection [67].

While cART does not preclude the use of any HC method, clinicians caring for women with HIV-infection must be aware of the potential drug–drug interactions between HC and antiretrovirals (Table 3) [6,63]. The integrase inhibitors have the lowest potential for significant interactions with HC [6,63].

Pregnancy

In the current era, with the combination of cART, appropriate use of intrapartum ZDV and fetal delivery methods, and infant prophylaxis, the risk of vertical transmission can be reduced to <1% [37]. For women with HIV who are planning pregnancy, ART should ideally be initiated, and virological suppression achieved, prior to conception [37]. Furthermore, pre-conception counselling should address reproductive options for couples planning pregnancy, including optimising management for sero-concordant couples and minimising risk of HIV transmission for sero-discordant couples [37,68]

Guidelines are available to assist practitioners with antiretroviral management of HIV-infected women who are planning pregnancy or are already pregnant (Table 4) [8,10,11,37]. For women already on ART, therapy should be continued as long as the regimen is

Table 4. Preferred antiretroviral therapy for HIV-infected pregnant women

Guideline source	DHHS [37]	EACS [8]	WHO [10,11]
Date of revision	2015	2015	2015[f] 2013[g]
Timing of ART	For women already on ART who present in the first trimester, continue current regimen if it is well tolerated and virological suppression has been achieved For women not on ART who present in the first trimester, consider initiating ART as soon as possible	For pregnant women already on ART continue current regimen unless that regimen is contra-indicated in pregnancy For women not on ART who present in pregnancy, initiate ART as soon as possible and no later than the beginning of the second trimester	ART should be initiated in all pregnant and breastfeeding women with HIV, regardless of CD4 count or WHO clinical stage (option B+)
Preferred regimens for ART initiation in pregnancy	NRTI backbones: • ABC/3TC[a] • TDF/FTC • ZDV/3TC Third agent: • ATV/r[b] • DRV/r[c] • EFV[d] • RAL[e]	Generally the same as for non-pregnant women but: • Do not initiate NVP in pregnancy • EFV can be started in pregnancy or continued in women who are already on therapy with HIV control • LPV/r and ATV/r are preferred PIs • **Do not** use d4T + ddI or triple NRTI combinations	Same as for non-pregnant adults: • TDF/FTC/EFV • ZDV/3TC/EFV • TDF/FTC/NVP • ZDV/3TC/NVP
Post-partum	ART is recommended for all HIV-infected individuals regardless of CD4 cell count Increase supports in immediate post-partum period as this represents a vulnerable time for ART adherence	ART is recommended for all HIV-infected individuals regardless of CD4 cell count	ART should be continued lifelong for all HIV-infected women

DHHS: Department of Health and Human Services; EACS: European AIDS Clinical Society; WHO: World Health Organization; ART: antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor; ABC: abacavir; 3TC: lamivudine; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine; ATV/r: ritonavir-boosted atazanavir; DRV/r: ritonavir-boosted darunavir; EFV: efavirenz; RAL: raltegravir; PI: protease inhibitor; NVP: nevirapine; LPV/r: ritonavir-boosted lopinavir; d4T: stavudine; ddI: didanosine.

[a] For patients who are HLA-B*5701 negative.

[b] Based on extensive experience in pregnancy; once-daily dosing.

[c] Twice-daily dosing required.

[d] Only if initiated after 8 weeks' gestational age.

[e] Associated with rapid virological suppression; twice-daily dosing required.

[f] Publication of timing of initiation recommendation.

[g] Publication of recommended regimens.

effective, tolerable and virological suppression has been achieved. In the virologically suppressed pregnant woman on EFV who presents in the first trimester, regimen modification is not required, as the period of potential teratogenicity has passed [37]. For pregnant women not on ART, therapy should be initiated as soon as possible, and chosen regimens should consider efficacy, safety and pharmacokinetics in pregnancy. The recommended agents in pregnancy in the USA differ from those in non-pregnant, HIV-infected adults [6,37], based on data for safety in pregnancy. The most recent recommendations include NNRTI-, PI- or INSTI-based regimens (Table 4). Several ARVs demonstrate pharmacokinetic alterations in pregnancy, and dose adjustments may be required [37]. Practitioners are encouraged to enrol pregnant women in the Antiretroviral Pregnancy Registry (www.apregistry.com) to assist with accumulation of data on the newer agents.

Pre-exposure HIV prophylaxis

While annual incidence of HIV is declining, there were still 2 million new diagnoses globally in 2014 [2]. Women account for approximately 20% of new HIV infections in the USA annually [3]. It is estimated that up to 20% of people with HIV in the USA are undiagnosed and/or unaware of being infected, thus contributing to ongoing propagation of the epidemic [69]. While condoms are effective in preventing HIV transmission, women may not always be in a position to advocate for barrier protection [1,3]. Recent advances in biomedical HIV prevention, including pre-exposure prophylaxis (PrEP), have resulted in several highly effective options to reduce HIV acquisition that fall within a woman's control.

Clinical trials have assessed the utility of pre-emptive antiretroviral use, typically with tenofovir or TDF/FTC, using various delivery mechanisms, to prevent HIV acquisition in HIV-negative women at high risk (Table 5) [70–78]. Results from oral PrEP trials in men at high risk of HIV acquisition have clearly demonstrated efficacy in preventing HIV [70,71,79]. However, results in women have been more inconsistent, which is likely to be due to variations in adherence (Table 5). The Partners PrEP study [70] was terminated prematurely after interim analysis demonstrated clear evidence of benefit for the intervention; there was no difference in efficacy between men and women. In the sub-population where adherence was assessed with drug-level monitoring, HIV risk reduction was 90% when tenofovir was detectable in plasma [70]. In TDF2 [71], overall efficacy for HIV prevention was 62.2%; with no difference in efficacy between men and women. In the Bangkok Tenofovir Study of injection drug users (IDU), subgroup analysis demonstrated higher adherence and efficacy in women versus men [72].

While Partners PrEP and TDF2 provided promising evidence that oral PrEP was an effective HIV-prevention strategy for heterosexual women at high risk, two subsequent, all-women trials have delivered more discouraging results (Table 5). In FEM-PrEP [73], interim analyses recommended study discontinuation due to futility, as there was no difference in HIV incidence between the intervention and placebo. Similarly, the VOICE study was halted early in the daily oral TDF and topical tenofovir gel groups due to lack of efficacy, while the oral TDF/FTC arm continued on to study conclusion; in the final analysis, there was no reduction in HIV transmission [74]. Lack of efficacy in FEM-PrEP and VOICE is likely to be related to reduced adherence compared to Partners PrEP and TDF2 (Table 5).

Table 5. Studies of pre-exposure prophylaxis (PrEP) in women at risk of HIV acquisition

Trial	Study design	Proportion of women	Intervention	Findings	Adherence
Partners PrEP [70]	Double-blind, placebo-controlled RCT 4758 HIV-serodiscordant couples in Uganda and Kenya; sero-positive partner not on cART 97–98% couples married	Woman was the HIV-negative partner in 52% of couples	Daily oral TDF or daily oral TDF/FTC or placebo	Overall efficacy was 67% for TDF and 75% for TDF/FTC In women, overall efficacy 71% for TDF and 66% for TDF/FTC; in men, overall efficacy 63% for TDF and 84% for TDF/FTC; no difference in efficacy between men and women	Detectable plasma tenofovir levels in 82%; PrEP associated with 90% risk reduction in this subgroup
TDF2 [71]	Phase II, double-blind, placebo-controlled trial 1219 heterosexual, HIV-negative men and women in Botswana 87.5–90% between 21–29 years 94% single	45.7%	Daily oral TDF/FTC *vs* placebo	HIV incidence 1.2 per 100 person-years in TDF/FTC group compared to 3.1 per 100 person-years in placebo group (overall efficacy 62.2%) No difference in efficacy between men and women	
Bangkok Tenofovir Study [72]	2413 injection drug users in Thailand	20%	Daily oral TDF *vs* daily oral placebo	Overall efficacy 48.9% for reducing HIV acquisition; in women, overall efficacy was 78.6% *vs* 37.6% in men Efficacy 73.5% in those with detectable plasma tenofovir levels.	Higher adherence in those >40 years and in women
FEM-PrEP [73]	Phase III, double-blind, placebo-controlled trial 2120 heterosexual women in South Africa, Kenya, Tanzania Mean age 24.2 years 30.0–31.8% married	100%	Daily oral TDF/FTC *vs* placebo	HIV incidence 4.7 per 100 person-years in TDF/FTC group vs. 5.0 per 100 person-years in placebo group (no reduction in HIV acquisition risk, HR 0.94)	Adherence was 95% by self-report; 88% by pill count; <40% had detectable plasma tenofovir levels
VOICE [74]	Phase IIb, double-blind, placebo-controlled trial 5029 heterosexual women in Eastern and Southern Africa Mean age 25.3 years Majority of women unmarried	100%	Daily oral TDF or daily oral TDF/FTC or daily oral placebo or daily 1% vaginal tenofovir gel or daily placebo vaginal gel	No difference in HIV acquisition risk between any of the five groups	Adherence 90% by self-report, 86% by returned pills and ≤30% by drug levels Having detectable tenofovir plasma levels associated with being >25 years (OR 1.62) or married (OR 2.25)
CAPRISA [75]	Double-blind, placebo-controlled trial 889 heterosexual women in South Africa Mean age 24.2 years 87.6–88.5% had a steady partner 5.4–5.8% married	100%	Daily 1% tenofovir vaginal gel or daily vaginal placebo gel	HIV incidence 5.6 per 100 person-years in tenofovir gel group *vs* 9.1 per 100 person-years in placebo group (39% overall efficacy)	Efficacy 54% when adherence >80%; reduced to 38% when adherence 50–80% and 28% when adherence <50%
FACTS 001 [76]	Phase III, double-blind, placebo-controlled trial 2029 heterosexual women in South Africa Mean age 23 years 88% unmarried	100%	Peri-coital 1% tenofovir vaginal gel or peri-coital placebo vaginal gel	No reduction in HIV acquisition risk between groups (IRR 1.0, 95% CI 0.7–1.4)	Only 20% reported using the product
ASPIRE [77]	Phase III, double-blind, placebo-controlled trial 2629 heterosexual women in Africa Median age 26 years 41% married 99.5% with steady partner	100%	Dapivirine impregnated vaginal ring (change every 4 weeks) *vs* placebo vaginal ring	HIV incidence 3.3 per 100 person-years in DPV group *vs* 4.5 per 100 person-years in placebo group (overall efficacy 27%) When excluded 2 sites with lower adherence, overall efficacy improved to 37% Efficacy 61% in women ≥25 years *vs* 10% in women <25 years	Overall adherence 82% by plasma DPV levels
RING [78]	Phase III, double-blind, placebo-controlled trial 1959 heterosexual women in South Africa and Uganda Median age 25 years 90% unmarried	100%	Dapivirine impregnated vaginal ring (change every 4 weeks) *vs* placebo vaginal ring	HIV incidence 4.08 per 100 person-years in DPV group *vs* 6.10 per 100 person-years in placebo (overall efficacy 30.7%, *P*=0.04); efficacy improved to 37.5% in subgroup of women ≥21 years of age	

PrEP: pre-exposure prophylaxis; cART: combination antiretroviral therapy; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; HR: hazard ratio; OR: odds ratio; DPV: dapivirine; *vs*: versus; IRR: incidence risk ratio; CI: confidence interval.

In FEM-PrEP, <40% of women assigned to TDF/FTC had detectable plasma tenofovir levels [73]. Women in this trial had a lower perception of HIV risk (with 50% of women reporting they had 'no chance' of acquiring HIV in the next 12 months) and were younger than women in Partners PrEP and TDF2, which may have contributed to poorer adherence and efficacy [80]. Similarly, self-reported adherence in VOICE was high among participants for whom drug levels were available, but ≤30% had detectable plasma levels of tenofovir [74]. Therefore, daily oral PrEP is probably an effective HIV prevention strategy in women who can adhere to therapy [80]. There may also be biological differences that result in reduced efficacy in women, including altered penetration of oral antiretrovirals into the female genital tract and potential interactions with hormonal contraception and pregnancy [80], although preliminary studies have failed to show alteration of PrEP efficacy with injectable depo-medroxyprogesterone-acetate (DMPA) [81]. Oral PrEP may also be less effective in younger women due to biological differences in the genital tract [80].

Adherence concerns with PrEP have also led to inconsistent efficacy results with use of vaginal tenofovir. In CAPRISA [75], a 1% vaginal tenofovir gel resulted in a 54% reduced incidence of HIV infection when adherence was >80%. There were no significant differences between the intervention and placebo with respect to renal, hepatic, pregnancy-related or genital adverse events, but women in the tenofovir gel group reported a higher frequency of diarrhoeal adverse events [75]. Preliminary results from FACTS 001 showed no reduction in HIV incidence between the two groups; however, tenofovir gel use was effective in the 20% of women who were adherent [76]. Similarly, the tenofovir gel arm of VOICE was discontinued prior to study conclusion due to lack of adherence and efficacy [74].

Several studies have attempted to determine if non-daily drug-delivery mechanisms might improve PrEP efficacy (Table 5). In ASPIRE, a sustained-release, dapivirine-impregnated (NNRTI) vaginal ring demonstrated a 27% overall efficacy in reducing HIV acquisition in women at high risk [77]. Similarly, the RING study has demonstrated overall efficacy of 30.7% in reducing HIV acquisition in preliminary analyses [78]; this improved to 37.5% in women ≥21 years of age.

Presently, clinical practice guidelines suggest daily oral PrEP with TDF/FTC should be considered for several populations, including heterosexual HIV-negative women at high risk [82]. As further evidence emerges regarding the safety and efficacy of alternative drug-delivery mechanisms for women, these guidelines are likely to evolve, and it will be important to consider not only efficacy of these delivery mechanisms, but also their acceptability for women.

Conclusions

Women represent more than one-half of the world's HIV-infected population, yet continue to be underrepresented in clinical trials of antiretroviral agents. Guidelines for treatment in women are extrapolated from study results in male populations. Enrolment and retention of women into clinical trials is feasible, and further studies focusing specifically on efficacy and safety of cART in women are required. Antiretroviral therapy in women must also consider sexual and reproductive health issues, including contraception, pregnancy, menopause, and strategies for HIV prevention.

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