



5th International Workshop on HIV & Women *from Adolescence through Menopause*

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Introduction

The 5th International Workshop on HIV & Women - *from Adolescence through Menopause* provides an opportunity for experts in the treatment and care of HIV positive women and the prevention of onward transmission of HIV to present the latest developments in the field.

The 2015 program included overview talks, oral abstract presentations, Q&A sessions, poster sessions and case study discussions. Topics covered included pregnancy, contraception, PrEP, adolescence and menopause, neurocognitive issues, behavioral issues, and the effects of gender and ethnicity on treatment and care.

This report summarizes the oral abstracts showing new research presented at the workshop, which include:

- Total and unbound pharmacokinetics of once-daily darunavir/ritonavir in HIV-1 infected pregnant women.
- Pharmacokinetics (PK) of etravirine (ETR) in HIV-1– infected pregnant women.
- Low prolactin and high 20alpha- HSD may contribute to cART- induced progesterone deficits in pregnancy
- Pregnancy rates among HIV-positive women using various forms of antiretroviral therapy and contraceptives in Kenya
- Progesterone increases are associated with HIV susceptibility factors in women.
- The association between HIV disclosure status and perceived barriers to care faced by women living with HIV: The ELLA Study
- A description of the demographic profile and reproductive choices of women living with HIV in the Russian Federation: cross-sectional survey.
- Factors associated with intimate partner violence amongst HIV-positive women in South-West Nigeria.
- The Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS): an evaluation of women-centered HIV care (WCC).
- Immunogenicity of the quadrivalent HPV vaccine in HIV positive women.
- Is the gender difference in virological response to ART declining over time?
- Gender and race differences in persistence of HIV treatment regimens.
- Genotypic analysis of the global clinical trial of treatment-naive women: WAVES.
- Peripartum hair levels of antiretrovirals predict viral suppression in Ugandan women.

PREGNANCY AND CONTRACEPTION

Pharmacokinetics in pregnancy

Physiologic changes during pregnancy can affect pharmacokinetics (PK). Two small studies evaluated the PK of darunavir/ritonavir (DRV/r) and etravirine (ETR) respectively in pregnant women. [1,2] In both studies drug exposure was altered in pregnancy, with lower concentrations reported for DRV and higher ones for ETR.

The DRV/r evaluation compared PK in pregnancy with that post partum. The study was open label, multicenter, phase 3b. Women were enrolled in the 2nd trimester of pregnancy and received DRV/r (600/100 mg twice daily or 800/100 mg once daily), ETR (see below) or rilpivirine, plus an optimized background regimen.

PK evaluations were performed in the 2nd and 3rd trimesters and 6 to 12 weeks post partum. Total and unbound DRV plasma concentrations and total ritonavir plasma concentrations were evaluated pre-dose and 1, 2, 3, 4, 6, 9, 12 and 24 hours post-dose. Data for participants receiving DRV/r 800/100 mg were reported.

Seventeen women were enrolled in the study: 5 black, 2 Latina, 7 white and 3 other. Sixteen had evaluable pharmacokinetic data.

The PK evaluation revealed reductions in total DRV AUC_{24h}, C_{min} and C_{max} of: 34% (LS mean ratio, 90% CI: 0.66, 0.60 to 0.74), 32% (0.68, 0.56 to 0.83) and 34% (0.66, 0.59 to 0.75) in the 2nd trimester, compared with post partum. The respective values were: 35% (0.65, 0.57 to 0.74), 50% (0.50, 0.35 to 0.73) and 31% (0.69, 0.63 to 0.77) in the 3rd trimester.

Unbound DRV concentrations were also lower during pregnancy but to a lesser extent. Compared with postpartum, DRV AUC_{24h}, C_{min} and C_{max} were decreased by: 24% (0.76, 0.67 to 0.85), 13% (0.87, 0.69 to 1.10) and 25% (0.75, 0.65 to 0.87) in the 2nd trimester; and 20% (0.80, 0.71 to 0.89), 38% (0.62, 0.43 to 0.90) and 16% (0.84, 0.74 to 0.96) in the 3rd trimester.

Ritonavir parameters decreased by approximately 45-50% overall in pregnancy compared with post partum.

Viral suppression <50 copies/mL increased and was maintained over time: 59%, 87%, 100% and 93% at baseline, 2nd trimester, 3rd trimester and postpartum respectively.

There were no deaths and 6 serious adverse events. All the events were considered to be pregnancy-related; only 1 (gestational diabetes) was considered possibly related to DRV/r. There were 3/16 infants born before week 37. All infants were HIV negative.

The PK (total concentrations) of ETR 200 mg twice daily was evaluated in a study of the same design. For this assessment 11/15 women had evaluable data.

ETR AUC_{24h}, C_{min} and C_{max} were higher by: 46% (LS mean ratio, 90% CI: 1.46, 1.12 to 1.90), 131% (2.31, 1.26 to 4.22) and 39% (1.39, 1.15 to 1.67) during the 2nd trimester compared with postpartum. For the third trimester the increases were: 28% (1.28, 0.98 to 1.69), 93% (1.93, 1.03 to 3.61) and 31% (1.31, 1.08 to 1.59).

Higher exposures of ETR did not result in an increase of adverse events. Four participants had serious adverse events, none of which were considered related to ETR. One participant had grade 1 treatment emergent atopic dermatitis that was considered possibly related to ETR. All infants were HIV negative.

The investigators noted that caution might be warranted with concomitant medicine or situations that could further increase ETR exposure.

Low prolactin and high 20alpha-HSD might contribute to ART-associated progesterone deficits in pregnancy

A Canadian study suggested that low progesterone (P4) levels observed in ART-exposed HIV positive pregnant women could be due to higher levels of 20αHSD induced by low hPL levels. [3]

ART has been linked to low birth weight, preterm delivery and other pregnancy complications. This research group had previously demonstrated that ART was associated with decreased levels of P4 mid-pregnancy in HIV positive women that correlated with birth weight.

For the study presented they investigated molecular mechanisms leading to ART-associated P4 level alterations in 33 HIV positive women receiving ART with 15 HIV negative women as controls.

The study assessed the expression levels of key enzymes of P4 synthesis and metabolism by PCR on placenta tissue. Plasma P4 and human prolactin (hPL) levels were quantified at week 33 to 37 of pregnancy by EIA. Human choriocarcinoma (BeWo) cells were treated with increasing doses of hPL for 24hours, 20αHSD expression and P4 levels were measured by PCR and EIA respectively. P4 levels in ART-exposed BeWo cells were assessed with or without 20αHSD inhibition.

The investigators found P4 levels to be significantly lower in the HIV positive compared to the HIV negative group: median 131.0 (IQR 93.3-158.9) vs 171.1 (139.6-198.8) ng/mL respectively, p=0.014.

They noted that placental expression of most P4 metabolism enzymes was similar between groups. Only the P4-eliminating enzyme 20αHSD was significantly higher in the HIV positive women: median 2.81 (IQR 0.89 to 26.05) vs 1.09 (0.623-1.56) arbitrary units in the HIV positive and HIV negative groups respectively, p=0.0084.

They found hPL, the main regulatory hormone for 20αHSD, to be significantly lower in the HIV positive group compared to controls: median 0.50 (IQR 0.38 to 0.72) vs 0.77 (0.48-0.89) ng/mL, respectively, p=0.043.

20αHSD expression significantly correlated with hPL levels in women's plasma at week 33 to 37 of gestation, p<0.0001. In BeWo cells hPL down-regulated 20αHSD expression and P4 production – this was dose-dependent, p<0.0001. ART-exposed BeWo cells produced significantly less P4 compared to controls: median 2.8 (IQR 2.5 to 3.1) vs 3.6 (3.5 to 3.7) ng/mL, p=0.028. Inhibiting 20αHSD activity (3.6 [3.4-4.0] ng/mL) restored P4 levels.

The investigators concluded that low P4 levels observed in ART-exposed HIV positive pregnant women could be the result of higher levels of 20αHSD induced by low hPL levels. They suggested that this observation might help to identify potential new therapeutic targets that could improve birth outcomes for HIV positive pregnant women receiving ART.

Pregnancy rates among women using ART and contraceptives in Kenya

Incident pregnancy rates in HIV positive women using the subdermal hormonal implant with EFV-based ART were 2.6 times higher than rates in women using NVP-based ART, according to a study conducted in western Kenya. [4]

Concerns have been raised by recent analyses showing EFV reduces the efficacy of subdermal contraceptive implants.

The aim of the Kenyan study was to determine whether pregnancy rates differed in women using implants or injectable depot medroxyprogesterone acetate (DMPA) and EFV- or NVP-based ART. It was a retrospective analysis

of a longitudinal cohort of women aged 18 to 45 years enrolled in HIV treatment facilities and followed from January 2011 to December 2013.

A total of 24,562 women contributed 94,716 observations to the analysis, with 3,331 incident pregnancies. Adjusted incident pregnancy rates among women using implants were 5.4 (95% CI: 1.9 to 8.8) and 2.1 (95% CI: 1.1 to 3.1) per 100 women years, for women receiving EFV- and NVP-based ART respectively. For DMPA users these rates were 13 (95% CI: 9.5 to 17) and 9.3 (95% CI: 8.0 to 11.0), respectively.

In the multivariate Cox proportional hazards models, the hazard of incident pregnancy among women using implants and receiving EFV- vs NVP-based ART was 2.6 (95% CI: 1.5 to 4.5), $p=0.001$. For DMPA the hazard of was 1.1 (95% CI: 0.87 to 1.4), $p=0.41$. But DMPA users had 3 times higher incidence pregnancy than implant users. The investigators noted that this was the largest cohort to date to suggest that the concomitant used of hormonal contraception with EFV-based ART might reduce the effectiveness of contraception.

Adolescents at increased risk of vertical transmission and poor pregnancy outcome in South Africa

Adolescent pregnant women had an increased risk of vertical transmission of HIV and poorer maternal and infant outcomes, compared to non-adolescent women, in a high HIV prevalence district in South Africa.

The study followed a cohort of HIV positive pregnant women and their infants at three urban sentinel surveillance facilities between January 2009 and March 2012. Enhanced routine individual clinical data were captured electronically. Adolescents were defined as 19 years or younger at their first antenatal visit. Multivariate models were used to compare outcomes between adolescents and women above 19 years of age.

The evaluation included 956 mother-infant pairs, of whom 65 (6.8%) were adolescents. At baseline the adolescents were a median age of 18 years (range 13 to 19) and the older women were 28 years (20 to 44). Their baseline CD4 count was 350 cells/mm³ (IQR 233 to 489) and this was similar between age groups, $p=0.16$. The median gestational age at booking was 22 weeks (IQR 17 to 27) and was similar between groups, $p=0.64$.

Treatment or PMTCT prophylaxis was according to WHO guidelines. ART eligible at <200 CD4 cells/mm³ before 2010 and <350 cells/mm³ from April 2010. Ineligible women received AZT from 28 weeks and single dose NVP in labor, and AZT from 14 weeks, single dose NVP and TDF/FTC to cover NVP tail during the respective time periods. Infants received NVP.

Adolescents were more likely to be unaware of their HIV status when booking: 75.4% vs 48.3%, adjusted risk ratio (aRR) 1.56 (95% CI: 1.34 to 1.82). They also were more likely not to be on ART at booking: 100% vs 82.8%. Median time of starting ART after first antenatal visit was 64 days (IQR 28 to 92) vs 36 days (IQR 20 to 62) for adolescents vs older women.

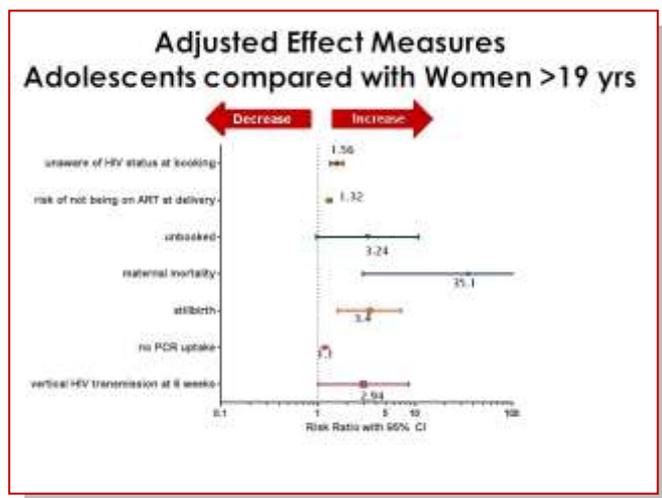


Figure 1: Adjusted effect measures adolescents compared with women >19 years.[5]

Adolescents were at increased risk of not receiving ART by delivery, aRR 1.32 (95% CI: 1.23 to 1.38), of being unbooked before labor, aRR 3.24 (95% CI: 0.96 to 10.9) and increased maternal mortality, aRR 35.1 (95% CI: 2.89 to 426).

Stillbirth among adolescent and older women was 9.4% and 4.5%, respectively, aRR 3.40 (95% CI: 1.61 to 7.20). Vertical transmission at 6 weeks was 8.3% and 3.1% amongst infants of adolescent and older women, respectively, aRR 2.94 (95% CI: 1.01 to 8.60).

The study investigators emphasized that interventions targeting adolescents are increasingly needed if South Africa is to attain its Millennium Development Goals.

HIV TRANSMISSION, CARE AND TREATMENT

Progesterone increases associated with HIV susceptibility in women

A US study suggested that increases in progesterone during the luteal phase of the menstrual cycle are associated with CD4 cells that have increased expression of the HIV co-receptor CCR5, higher activation levels, and an increased response to stimulation. [6]

Previous studies have suggested that native progesterone and progestin-based hormonal contraception might increase women's risk for sexual HIV transmission. The mechanism for this is unclear. This study investigated whether increased progesterone levels during the luteal phase increase markers of susceptibility in HIV target cells.

The investigators isolated peripheral blood mononuclear cells (PBMCs) from whole blood of 7 women at 5 study visits throughout their normal menstrual cycles. Using flow cytometry, PBMCs were tested for expression of CCR5 and the activation marker CD38.

PBMCs were stimulated *ex vivo* for 5 hours in the presence of golgi inhibitors. Intracellular production of TNF- α , IL-2, IFN- γ was detected using flow cytometry. Plasma estradiol and progesterone were measured at each time point using a luminex multiplex assay. A sustained rise in plasma progesterone levels marked the beginning of the luteal phase of the menstrual cycle.

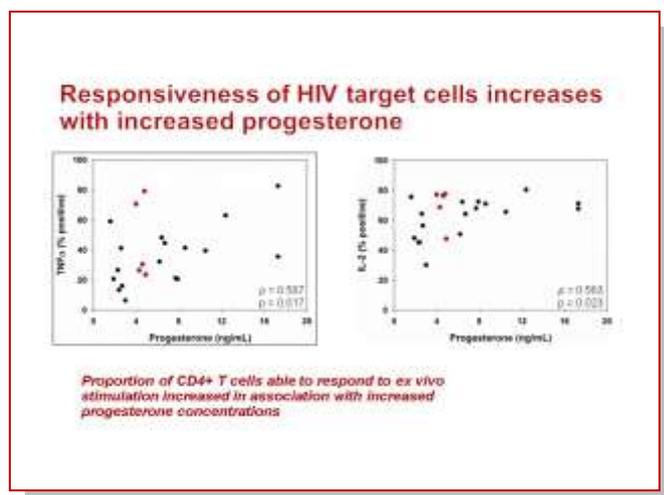
The women completed 28 total study visits: 1 woman made 5 visits; 5 women made 4 visits; and 1 woman made 3 visits. There was no detectable sustained rise in progesterone in 2/7 women.

The investigators found that the proportion of CD4 memory cells expressing CCR5 increased during the luteal phase of the menstrual cycle, $p=0.012$. The proportion of CD4 memory cells expressing CD38 increased in 6 of 7 women during the luteal phase but this was not statistically significant.

The proportion of *ex vivo* stimulated CD4 T cells with detectable intracellular TNF- α increased from 31% to 52%, $p=0.006$, from the follicular to the luteal phase while production of intracellular IL-2 and IFN- γ did not.

Increased populations of TNF- α producing cells were associated with higher plasma progesterone levels, $p=0.04$.

Figure 2: Responsiveness of HIV target cells increases with increased progesterone [6]



The investigators noted that the increase in TNF- α production was almost exclusively in cells, which were also expressing IL-2 or both IL-2 and IFN- γ . Also that time points with detectable increases in TNF- α production were the same or immediately preceding those where CCR5 and CD38 expression increased in 6 of 7 women. They did not find estradiol levels to be associated with changes in CCR5, CD38, or *ex vivo* cytokine production.

"Knowing if these progesterone effects exist in the genital mucosa of women could be an important measure for identifying risk factors of progestin-based hormonal contraceptives", they concluded.

Association between HIV disclosure and perceived barriers to care: The ELLA Study

Non-disclosure of HIV status increased barriers to accessing healthcare services by women in the ELLA study. [7] HIV status disclosure is associated with improved health outcomes. Women are less likely than men to disclose their status.

ELLA was a cross sectional study, non-interventional cohort study conducted in 4 global geographic regions (Latin America, China, Central/Eastern Europe, and Western Europe/Canada) that looked at global and regional barriers to access to care affecting HIV positive women. The sub-analysis presented examined the relationship between perceived barriers to care and disclosure of HIV status.

ELLA enrolled women aged 18 years of age and above who had HIV for at least 3 months. Women were offered the opportunity to participate (non-random sequential sampling frame design) at routine clinic visits. They completed questionnaires at a single time point. This included the self reported 12-item Barriers to Care Scale

(BACS) and the Overall Health Assessment.

The 12 items in the BACS are: 1) Long distance to medical facilities; 2) Declined direct care to a person with HIV; 3) Lack of trained and competent HIV provider; 4) Lack of transportation; 5) Lack of mental health HIV provider; 6) Lack of psychological support; 7) Community HIV knowledge; 8) Community stigma; 9) Lack of employment opportunities; 10) Lack of supportive work environment; 11) Personal financial resources; and 12) Lack of adequate housing.

The participants used a 4-point severity scale from 1) no problem at all to 4) major problem; scores greater than 2 were considered significant. Women who answered 6 or more BACS items were included in the analysis and categorized by HIV disclosure status.

Disclosure status was defined as: not disclosed; disclosed to close/intimate relations; disclosed extended relations; or full disclosure.

Between-group comparisons were assessed using Mann-Whitney test (for continuous variables) or Chi-square test (for categorical variables).

Of 1945 women enrolled, 1929 were included in the analysis: 1724 disclosed and 205 not disclosed. Of disclosed participants: 1481 (85.9%) had disclosed their HIV status to close/intimate relations, 166 (9.6%) to extended relations and 77 (4.5%) had full disclosure.

The analysis revealed, disclosed participants were: younger (mean 40 vs 42 years respectively for disclosed and not disclosed, $p=0.008$); diagnosed with HIV for longer (median 8.0 vs 6.3 years; $p=0.02$; more likely to live with a partner (57.9% vs 32.7%, $p<0.0001$), and received more support from family or friends (64.4% vs 23.4%; $p<0.0001$), compared to those who were not disclosed.

Mean BACS severity scores for medical and psychological service barriers and most personal resource barriers were significantly lower for the disclosed group: 1.6 to 1.7 for medical/psychological services; and 1.9 to 2.6 for personal resource barriers compared with the not disclosed group (1.8 to 2.1 and 2.4 to 3.9, respectively; $p=0.02$ for all comparisons).

Community HIV stigma and the lack of community HIV knowledge, employment opportunities, supportive work environments, and personal financial resources were reported as severe (mean severity score >2) barriers to care by both groups.

The investigators observed statistically significant differences in BACS item severity scores between disclosure groups for: the declination to provide direct care to people with HIV ($p=0.025$), the lack of trained health care professionals in HIV ($p=0.0003$), lack of transportation ($p<0.0001$), lack of mental health healthcare providers ($p<0.0001$), lack of psychological support ($p<0.001$), lack of supportive work environment ($p=0.0016$), personal financial resources ($p=0.0038$), and lack of adequate/affordable housing ($p<0.0001$).

Preliminary Quality of Life analysis found significant differences ($p<0.03$) between groups for trouble with attention on activities, feeling calm and peaceful, tired, enough energy and feeling bad.

The investigators concluded that contributing factors to women's non-disclosure and lack of support need further investigation to improve access to care. "As clinicians, we should consider discussing and addressing disclosure", they wrote.

Demographic profile and reproductive choices of HIV positive women Russia

In the first reported epidemiological study of this type for HIV positive women in Russia, IDU-associated infection and HCV co-infection were common, and younger women had fewer vertical transmissions than older ones. [8]

Women represented approximately half of new HIV infections in the Russian Federation in 2013, when the study was conducted) and vertical transmission remained high.

The study was a cross-sectional, questionnaire-based survey of HIV positive women aged ≥ 18 years attending a routine clinical visit in 10 sites across the country: Moscow, St Petersburg, Volgograd, Vladikavkaz, N. Novgorod, Kurgan, Irkutsk, Novosibirsk, Chelyabinsk, and Vladivostok.

The survey collected descriptions of: demographics, HIV disease characteristics, comorbidities, reproductive choices, pregnancy status, ART regimen and mode of transmission.

A total of 1131 women were enrolled, their mean age was 32.2 years (SD 8.8). Most women (73.3%) were aged 18 to 35 years. About 70% were in relationships, of which about half were with an HIV positive partner. The majority (76.4%) had attended school or college and 60.2% were employed. Most women (71.6%) had acquired HIV through sexual contact and 24.7% through IDU.

Classified by Russian HIV stages at enrollment: 48.8% of women were subclinical and 47.5% had HIV-related conditions. Mean duration of HIV infection was 60.7 months (SD 52.4). Mean CD4 count was 481.4 cells/mm³ (SD 243.0): 40.9% had >500 cells /mm³, and 70.2% had >350 cells /mm³. Median viral load was 225.0 copies/mL.

Just over 80% reported one sexual partner, with 55.4% reporting unprotected sex within 3 months before enrollment. Over 60% of women reported using male condoms for contraception, less than 2.0% used oral contraceptive pills. Nearly 40% did not use any contraceptive method. The proportion using no contraception

was significantly higher in women aged 18 to 25 years (n=282) vs 26 to 35 year olds (n=547), 52.8% vs 34.6% respectively, p<0.0001.

At study enrollment, 18.1% women were pregnant. Most current pregnancies were planned (64.9%), but the majority of previous ones were unplanned (61.8%). More women aged 18 to 25 years received ART to prevent vertical transmission (85.3% in pregnancy, 88.2% during delivery and 84.3% post-partum) than those aged 36 to 45 years (63.8% in pregnancy, 69.0% during delivery and 67.2% postpartum), p<0.05. A smaller proportion of younger women had HIV-infected newborns (2.0% vs. 29.3%), p<0.0001.

The most common co-morbidity was hepatitis C (39.3%).

The majority of women (64.4%) received ART regimens: 91.8% containing NRTIs, 75.3% boosted PIs 18.7% NNRTIs and 6.5% integrase inhibitors. No missed doses were reported in the last 7 days by 85.9% of women and in the last month by 74.0%.

The investigators noted that these results are useful for guiding management and resources to support HIV positive women in Russia women and reducing onward transmission.

Intimate partner violence among HIV positive women in South West Nigeria

Over half of women interviewed experienced intimate partner violence (IPV) after disclosing their HIV status in a study looking at prevalence, forms and factors associated with IPV conducted in south western Nigeria. [9]

The investigators noted that domestic violence towards Nigerian women had increased from 21% in 2011 to 30% in 2013. Intimate male partners are responsible for an estimated two-thirds of these incidents. A correlation between HIV positive status and domestic violence has previously been shown.

This cross-sectional survey was conducted at the ART clinic of a health facility serving >1,500 women HIV positive women. The study used a structured questionnaire to collect socio-demographic and intimate relationship data. This included information on IPV before and after HIV status disclosure and consequence(s) of the experience(s). IPV was defined as physical, sexual, and psychological according to WHO definitions. The investigators used multivariate logistic regression analysis to analyze factors associated with IPV.

A total of 328 HIV positive women consented to be interviewed, (approximately 22% accessing care at the facility). Mean age of respondents was 33.1 years (range 18 to 55). Almost 70% knew their partner's HIV status (32.6% HIV-positive and 36.9% HIV-negative).

More than one third (35.1%) of women experienced some form of IPV. Psychological violence was most frequent (experienced by 53.9% of respondents), followed by physical (34.8%) and sexual violence (33.7%).

About two thirds (206/328, 62.8%) of women had disclosed their HIV status rate to their partners. Of these 79/206 (38.3%) had experienced pre-disclosure IPV, with 40/79 (50.6%) experiencing physical, 39/79 (49.4%) sexual and 62/79 (78.5%) psychological violence.

Over half (115/206, 55.8%) experienced IPV post-disclosure, p=0.0004 (vs pre-disclosure). With 58/115 (50.4%) of women experiencing physical, 71/115 (61.7%) sexual and 113/115 (98.2%) psychological violence.

The investigators reported correlates for post-disclosure IPV were:

- HIV positive partner (p<0.0001)
- Older partner age ≥40yrs (p<0.0001)
- Lower level (none or primary level) of partner's education (p=0.004)
- Higher alcohol intake by partner (p=0.001)
- Cohabitation (p=0.002)
- Marriage (p=0.03)
- More than 1 current sexual partner (for male partner p=0.02, for respondent p< 0.0001)

Overall the investigators concluded that HIV status disclosure increases the risk of IPV in HIV positive women. They recommended community-wide IPV education during HIV testing and counselling, and focus on HIV positive male partners in high-burden areas. Couples' HIV testing and counselling should also be encouraged, to minimize harm to women living with HIV, they said.

The Canadian HIV Women's Sexual and Reproductive Health Cohort Study

Women were generally satisfied with the care they received from their HIV clinic and doctor according to a report from the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS). [10] The study also found that the degree to which their HIV care was women-centered varied by province.

CHIWOS is a five-year, national, multi-site, interdisciplinary, community-based research, longitudinal cohort study. The primary objectives are to: 1) look at the proportion, distribution and patterns of women-centered care (WCC) among HIV positive women in British Columbia, Ontario and Quebec, and 2) determine the correlates of WCC and impact on overall, mental, sexual and reproductive health outcomes.

CHIWOS is enrolling over 1,400 women (self-identified, transgender inclusive) with HIV, aged 16 years and above in British Columbia, Ontario and Quebec – where 82% of Canadian women with HIV live. The study is expanding

to additional provinces.

Participants complete a peer research associate-administered questionnaire at baseline and at 18-months that includes questions concerning: medical history, use of clinical and social services and WCC, health outcomes, substance use, experiences of violence, stigma and discrimination, food and housing security, and other social determinants of health.

As of 13 February 2015, the study had enrolled 1,285 participants: 320 from British Columbia (25%), 685 from Ontario (53%) and 241 from Quebec (22%). Median age is 42 years (IQR 35 to 50).

Participants represent diverse communities: 24% identified as Indigenous, 29% as African, Caribbean, or Black Canadian, and 39% as Caucasian. Overall, 38% and 31% reported incarceration history of IDU respectively; 32% and 9% reported being diagnosed with hepatitis B and C co-infection respectively.

Overall, 82% of women were currently taking ART and 76% reported an undetectable viral load. Of the 1,200 women who received HIV medical care in the last year, 92% and 55% were satisfied with the care they received from their HIV clinic/doctor and perceived it to be women-centered respectively.

The quadrivalent HPV vaccine in HIV positive women

A Canadian study found HPV seroconversion rates that were higher than anticipated in HIV positive women who received the quadrivalent HPV vaccine but their peak antibody levels were significantly lower than those of HIV negative women. [11]

HPV vaccines have shown good immune response and effectiveness in preventing HPV infection and cervical dysplasia in HIV negative women but limited data is available for HIV positive women.

The study was open label, multi-centered with the primary objective to evaluate seroresponsiveness to the quadrivalent HPV vaccine in HIV positive girls and women. The study was launched in November 2009 and completed enrollment in December 2012. The duration for each participant was 27 months.

The investigators used Linear Array to determine genotype specific HPV (DNA) infection. HPV antibody levels were measured by Merck cLIA assay to HPV 6/11/16/18 at baseline, and months 2, 7 (1 month post 3rd vaccine), 12, 18 and 24.

A total of 190 women who received 3 doses of vaccine within 1 year and had 1-month post 3rd vaccine antibody data available were included in this per protocol analysis.

The investigators used generalized linear models to estimate the ratio of geometric mean titers (GMT) between those with suppressed (<50 copies/mL) and unsuppressed viral load at baseline.

HPV type-specific analyses were limited to those who were antibody negative at baseline and DNA negative up to month 7 for ≥ 1 HPV type.

Median age of the participants was 39 years (IQR 32 to 45); 44% were black, 37% white and 19% other ethnicities. Median CD4 count at time of first vaccination was 520 cells/mm³ (IQR 390 to 710), CD4 nadir was 230 cells/mm³ (IQR 110-320) and 75% had a suppressed viral load.

The overall seroconversion rate was 98.9% (96.1 to 99.0).

When compared to historical general population GMTs, HIV positive women aged 15 to 26 had significantly lower GMTs at month 7 for HPV-11 ($p < 0.001$) and HPV-18 ($p < 0.01$). At month 24, GMTs were significantly lower for HPV-11 ($p = 0.02$), HPV-16 ($p < 0.01$) and HPV-18 ($p < 0.001$).

Among women aged 24 to 45 all comparisons of serologic response were significant at month 7 ($p < 0.0001$), but HIV positive women only had significantly lower GMTs at month 24 for HPV-11 ($p = 0.05$).

HIV positive women with suppressed viral load at first vaccination had a 2 to 3 fold higher antibody response compared with those whose viral load was unsuppressed – this response was sustained to the end of the study.

SEX AND GENDER

Is the gender difference in virological response to ART declining over time?

A study conducted in the UK found that although rates of virological failure are low in people starting first line ART, women and men who have sex with women (MSW) remain more likely to experience this than men who have sex with men (MSM). [12] There was no evidence that the gap is narrowing for those starting ART in more recent years.

The study was in ART-naive participants with a sexual risk for HIV transmission attending the Royal Free Hospital, London. Those included started ART between January 2001 and July 2013 and had documented viral load measurements at 12 to 18 months and 24 to 30 months from initiation.

The investigators assessed the proportion of participants with viral load non-response (>200 copies/mL) by gender/sexual orientation group and by year of ART initiation. Logistic regression adjusted for ethnicity, age and ART regimen was used to evaluate whether the association between gender/sexual orientation and virological failure changed over time.

A total of 1606 participants were included: 864 were MSM, 283 MSW and 458 were women. For MSM, MSW and women respectively: 1%, 52% and 66% were of black African ethnicity; 83%, 27% and 15% were white; and 16%, 22% and 22% were other. Median baseline age was 38, 41 and 36 years, CD4 was 268, 160 and 205 cells/mm³ and viral load was 5.0, 5.0 and 4.8 log copies/mL. First line ART regimens were similar with slightly more women starting with PI-based regimens (49%) compared to the other two subgroups (44%).

For MSM, MSW and women respectively: 7%, 14% and 21% had viral load >200 copies/mL at 12 months and 9%, 14% and 20% at 24 months, all comparisons p<0.0001.

Across all three subgroups, proportions of participants with virological failure after 12 and 24 months of ART were improved in later years, all comparisons p<0.001.

For MSM, MSW and women respectively, change in 12-month viral load non-response per calendar year by gender/sexual orientation (adjusted OR): 0.77 (95% CI: 0.07 to 0.84), 0.85 (0.75 to 0.96) and 0.86 (0.79 to 0.93), p=0.15. Change in 24-month viral load non-response per calendar year by gender/sexual orientation (adjusted OR): 0.73 (95% CI: 0.66 to 0.81), 0.82 (0.71 to 0.94) and 0.86 (0.78 to 0.95), p=0.072.

The investigators noted that women had more ART disruptions (switched or interrupted treatment) so non-adherence might contribute to the observed differences. They also suggested that poorer viral load outcomes in women and MSW might be related to: socio-economic status, time in the UK, family circumstances, psychological factors and co-morbidities.

These findings show that even in a high income setting with universal free access to healthcare, women are at higher risk of virological failure. Emphasis should be placed on improved/tailored support for HIV positive women.

Gender and ethnicity differences in duration of ART

A related US study suggested gender and ethnicity differences in ART disruption might explain some of the differences seen in treatment outcomes among HIV positive women and especially African American women. [13]

The University of Alabama at Birmingham conducted the study to evaluate differences in ART discontinuation by gender and ethnicity. It was a retrospective medical chart review including ART naive, HIV positive patients, aged 18 and above, attending an urban outpatient clinic in Birmingham, AL between January 2004 and February 2009. The evaluation included: socio-demographic and clinical factors, ART regimens with start and stop dates, and reasons for change.

Regimens were considered discontinued or changed if any antiretroviral within the regimen was discontinued or if any additional one was added.

The investigators used Cox proportional hazards regression to model time to individual regimen discontinuation and Poisson regression to model the numbers of days of treatment interruption (≥ 14 days).

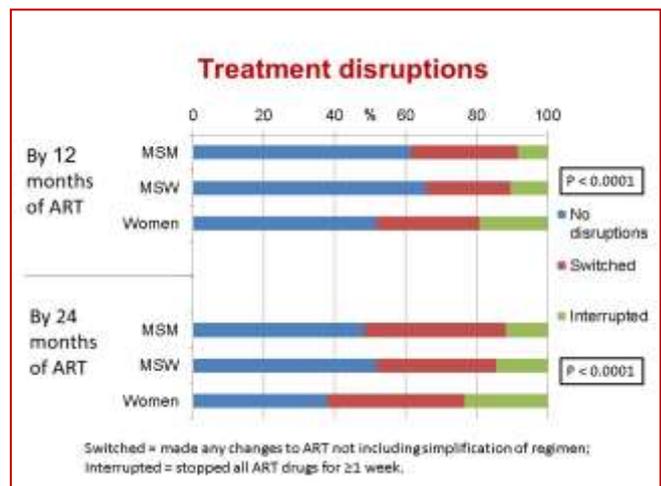
There were 422 HIV positive participants included in the analysis: 90 (21%) were women and 226 (54%) were African American (64 African American women, 162 African American men, 22 white women, 151 white men and 23 with ethnicity other/unknown).

Overall 243 (58%) participants discontinued or changed at least one antiretroviral during a median follow up of 2.8 years. With white men – who had the lowest discontinuation rate – as reference the hazard ratios for discontinuation for African American women, African American men and white women were respectively: 1.6 (95% CI: 1.2 to 2.2), p=0.004; 1.4 (1.1 to 1.8), p=0.011; and white women 1.2 (0.70 to 2.0), p=0.538.

The most frequent reasons for discontinuing ART for African American women were: poor adherence (57.5%), other medical conditions (15.1%), and GI toxicity (9.6%).

The overall treatment interruption rate was 13.9 days per year, with African Americans interrupting treatment for more days per year than white participants: 17.5 vs 9.4 days/year, $p=0.05$. The investigators suggested that the differences in rates of discontinuation might account for some of the less favorable ART outcomes observed in African American women.

Figure 3: Percentage interrupting treatment before 12 months over time [13]



Genotypic Analysis of the Global Clinical Trial of Treatment-naïve Women: WAVES

Pre-existing NRTI and NNRTI resistance was common in the Women AntiretroViral Efficacy and Safety study (WAVES) cohort of treatment-naïve women with a global distribution of HIV subtypes. [14]

WAVES is the first women-only, international, randomized, double blinded, phase 3 clinical trial designed to evaluate the safety and efficacy of two recommended regimens.

Data were presented from an evaluation of the global distribution of women in WAVES and their HIV subtypes, and the frequency of antiretroviral resistance in the participants.

HIV positive, ART naïve adult women were enrolled in this double blind, 48 week, clinical trial and randomized 1:1 to once daily elvitegravir (EVG)/cobicistat (COBI)/ FTC)/TDF or ritonavir (RTV) boosted atazanavir (ATV) plus FTC/TDF. Women with viral load >500 copies/mL, estimated GFR>70 mL/min and previous ART were eligible.

Genotypic analyses of protease and reverse transcriptase were conducted. Monogram Biosciences predicted drug susceptibilities.

A total of 575 women were enrolled and received study drugs in 12 countries: Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, UK, and US.

The analysis found subtype A to be the most prevalent (46%) followed by subtype B (26%). The investigators saw distinct regional demographic differences (North America, Europe, Africa, Asia) in subtype distribution. Subtype A was predominant in Russia and Uganda, and subtype B in the US.

Transmitted resistance was seen in 34% of women. Primary NNRTI and NRTI resistance was frequent (both 20%) but primary PI resistance was rare (1.7%). The A62V substitution in reverse transcriptase was highly prevalent in Russia (44.3%, 85/192).

Predicted resistance to EFV and NVP was seen in 10% and 3% of participants with subtype B and non-B subtype respectively.

Peripartum hair concentrations of antiretrovirals predict viral suppression

Hair concentrations of EFV and LPV were strong predictors of viral suppression at delivery and 24 weeks postpartum in the PROMOTE trial. This method of measuring drug exposure was a better predictor than self-reported adherence and pretreatment viral load. [15]

Hair concentrations have previously been shown to predict viral suppression but this phenomenon had not been evaluated in pregnant and breastfeeding women.

PROMOTE (an open label, randomized trial to investigate whether LPV reduces rates of placental malaria) enrolled HIV positive, ART-naïve pregnant Ugandan women at 12 to 28 weeks gestation who were randomized to start LPV/r- or EFV-based ART. The LPV/r dose was increased from 400/100 mg twice daily to 600/150 mg twice daily from 30 weeks gestation to delivery.

Viral load was tested at screening, delivery and 24 weeks postpartum. Self-reported adherence was recorded for three days before each four-weekly study visit.

The investigators collected hair samples at 30 to 34 weeks gestation and 10 to 25 weeks postpartum from women on ART for at least 6 weeks. EFV and LPV hair concentrations were measured using liquid chromatography/tandem mass spectrometry. Multivariate logistic regression models were used to examine predictors of viral suppression (<400 copies/mL) at delivery and 24 weeks postpartum.

At baseline, 325 women, were a mean age of 30 years (SD 5.4) with median CD4 cell count was 366 cells/mm³ (IQR 270 to 488). Median time on ART at delivery was 17 weeks (IQR 14 to 21). Mean self-reported adherence was 100% in both arms.

Viral suppression was achieved by 98% and 87% at delivery and 93% and 91% at 24 weeks postpartum, in women receiving EFV (n=162) and LPV (n=163) respectively.

The investigators noted that 88% of women were breastfeeding at 24 weeks postpartum and one infant in the LPV/r was HIV infected.

In multivariate models including self-reported adherence and pretreatment viral load, hair concentrations were the strongest predictor of viral suppression at delivery: aOR per doubling in concentration was 1.86 (95% CI: 1.14 to 3.1), p=0.0, and 1.90 (95% CI: 1.33 to 2.7), p=0.0004 for EFV and LPV respectively. At 24 weeks postpartum these values were: aOR 1.81 (95% CI: 1.22 to 2.7), p= 0.003 and aOR 1.53 (95% CI: 1.05 to 2.2), p=0.03.

The investigators noted the higher rate of viral suppression at delivery in the EFV arm is consistent with published results from PROMOTE. They found that hair collection was highly acceptable (84%) among this group of Ugandan women.

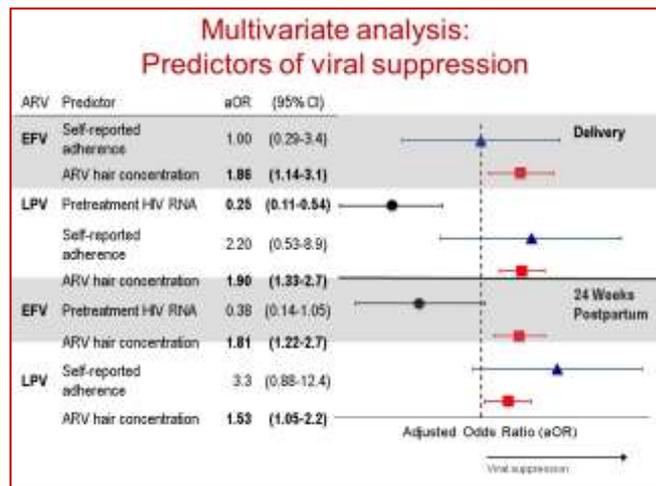


Figure 4: Multivariate analysis predictors of viral suppression [15]

NEXT YEAR:



REFERENCES

All references from the program and abstracts 5th International Workshop on HIV & Women,

The abstracts are online at: <http://www.infectiousdiseasesonline.com/abstract-book/>

Links to presentations <http://www.infectiousdiseasesonline.com/presentation/>

1. Crauwels HM et al. Total and unbound pharmacokinetics of once-daily darunavir/ritonavir in HIV-1– infected pregnant women. Oral abstract 01.
2. Ramgopal M et al. Pharmacokinetics (PK) of etravirine (ETR) in HIV-1– infected pregnant women. Oral abstract 02.
3. Papp E et al. Low prolactin and high 20alpha- HSD may contribute to cART- induced progesterone deficits in pregnancy. Oral abstract 03.
4. Patel R et al. Pregnancy rates among HIV-positive women using various forms of antiretroviral therapy and contraceptives in Kenya. Oral abstract 04.
5. Fatti G et al. Adolescents at Increased Risk of Mother to Child Transmission of HIV in South Africa. Oral abstract 05.
6. Swaims AY et al. Progesterone increases are associated with HIV susceptibility factors in women. Oral abstract 06.
7. Loufty M et al. The association between HIV disclosure status and perceived barriers to care faced by women living with HIV: The ELLA Study. Oral abstract 07.
8. Voronin EE et al. A description of the demographic profile and reproductive choices of women living with HIV in the Russian Federation: cross-sectional survey. Oral abstract 09.
9. Ezebuka E et al. Factors associated with intimate partner violence amongst HIV-positive women in South-West Nigeria. Oral abstract 11.
10. Loufty M et al. The Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS): an evaluation of women-centred HIV care (WCC). Oral abstract 12.
11. Money D et al. Immunogenicity of the quadrivalent HPV vaccine in HIV positive women. Oral abstract 8.
12. Burch LS et al. Is the gender difference in virological response to ART declining over time? Oral abstract 14.
13. Kempf MC et al. Gender and race differences in persistence of HIV treatment regimens. Oral abstract 15.
14. Hodder S et al. Genotypic analysis of the global clinical trial of treatment-naive women: WAVES. Oral abstract 16.
15. Koss CA et al. Peripartum hair levels of antiretrovirals predict viral suppression in Ugandan women. Oral abstract 17.