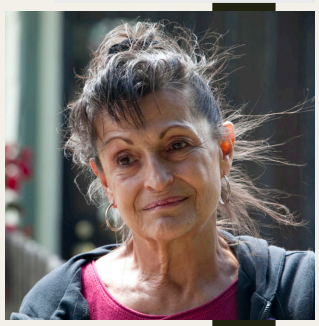
CONSIDERATIONS FOR THE HIV POSITIVE WOMAN DURING MENOPAUSE



Dr. Sharon Walmsley
University Health Network , Toronto, Ontario
Canadian HIV Clinical Trials Network

Objectives

- To review the epidemiology of HIV and older women
- To review the diagnosis and management of menopause in WLWH
- To review what is known about the unique features of menopause in WLWL
- To discuss the impact of menopause on the outcome of HIV in women

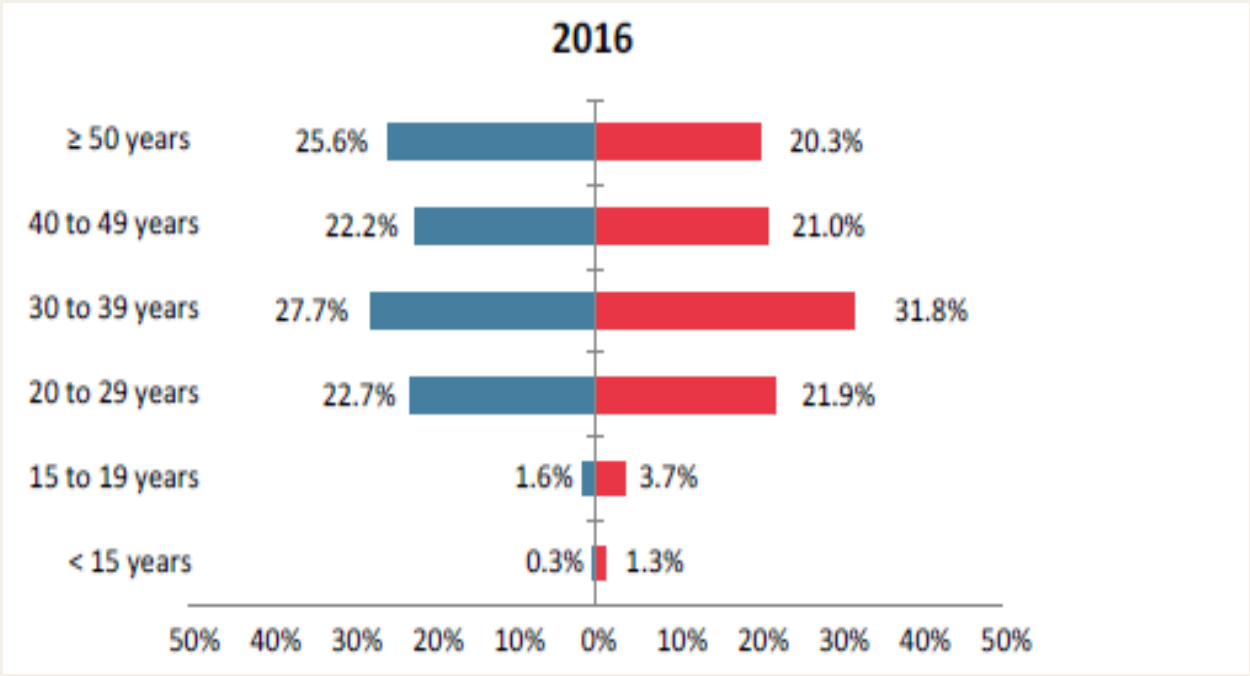
No conflicts in relation to this talk but I do have lived experience

The HIV population is aging

- New diagnosis in older persons
- Improved survival of those with HIV infection

HIV in Canada—Surveillance Report, 2016

AC Bourgeois[1], M Edmunds[1], A Awan[1,2], L Jonah[1], O Varsaneux[1], W Siu[1]



Do we meet the first 90 ?
Are older women being tested for HIV?

- 15–30% of women ages 55 and older have previously been tested for HIV
  - Not perceived to be at risk
  - Women don't want to be tested
  - Concern re: intimate partner violence
  - Sexual activity (risk) often not discussed
  - Symptoms attributed to "aging" or "menopause" or "depression"
- If tested often late when present with OI and have high mortality and poor outcomes

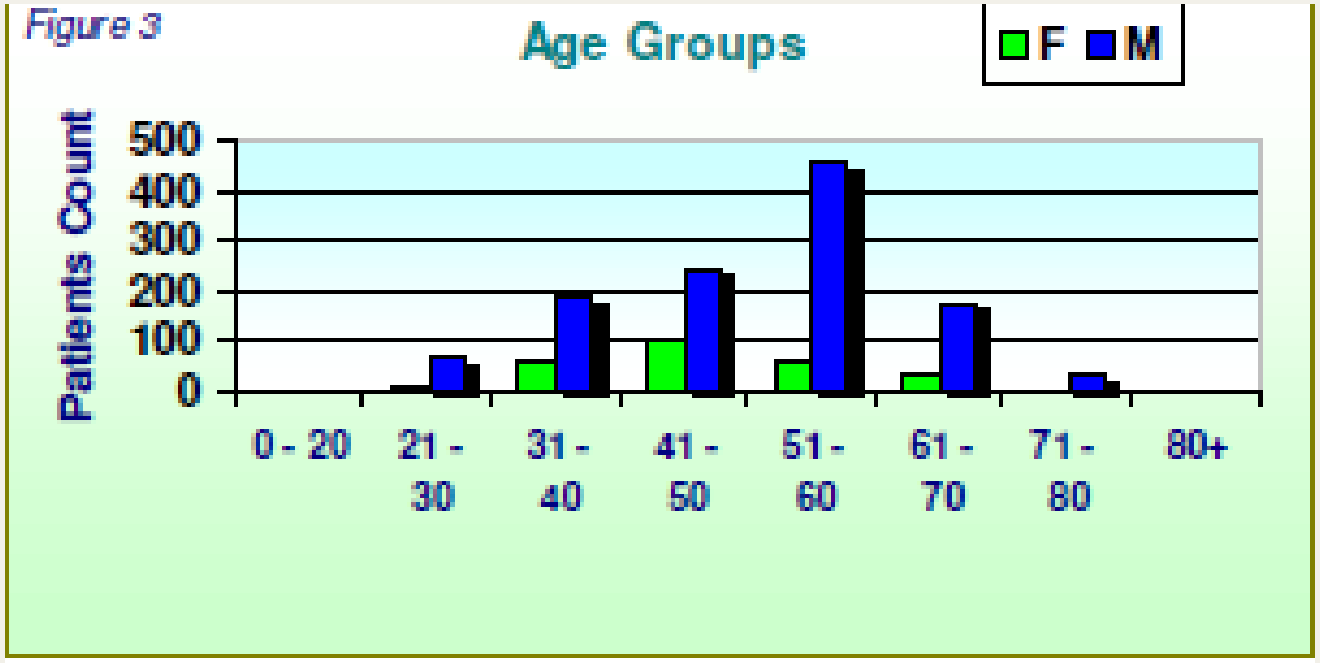
Siegel K et al, AIDS Care 1999; 11(5):525-35; Harawa NT et al, Sex Trans Dis; 2011; 38(12):1110; Akers A, J woman Health 2007 ;16(6) 842

Are older women at increased risk of HIV acquisition ?

- Behavioral
  - **Midlife changes in relationship status**
  - **Power imbalances, mental health issues, substance use**
  - **Less condom use and other prevention methods**
- **Biological**
  - **Elevated % R5+CD4+ T lymphocytes in cervix may increase the risk for HIV acquisition in post-menopausal vs pre-menopausal women.**
  - **Elevated R5 expression on cervical CD4+ T cells may be related to aging.**
  - **Further research is needed to determine if these changes are primarily due to aging or changes in female sex hormones that occur at menopause**.

Sherman, J Women Aging, 2005; 17(3): 41-55; Cornelius JB, J Assoc Nurses in AIDS Care; 2008, 19(1): 16-27; A Meditz, JAIDS, 2012:59(3) 221-28.

Our populations of Women living with HIV are aging

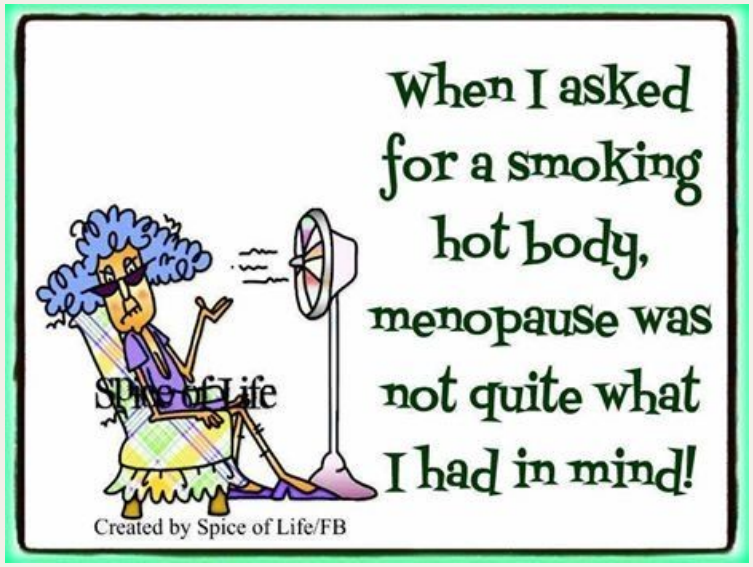


Median age men = 52

Median age women= 48

Active patients – UHN Toronto

Menopause


When I asked for a smoking hot body, menopause was not quite what I had in mind!
Spice of Life
Created by Spice of Life/FB

What is Menopause ?

- defined as the absence of menstrual periods for 12 months.
- Loss of ovarian follicular activity
- The process of *menopause* does not occur overnight, but rather is a gradual process.
- The peri-menopausal transition period is a different experience for each woman.

How do you determine the time of menopause?

- By history
- Endocrine hormone levels- LH, FSH
- Anti- Mullerian hormone levels- AMA- produced by ovarian follicules, measure of ovarian reserve

- the average age is 51 in the United States

What have been the issues related to HIV and Menopause?

- Does it occur earlier?
- Do HIV infected women have more symptoms than the general population?
- How can you differentiate symptoms of menopause from those of HIV?
- How should it be managed?
- Is this a time of increased comorbidity?
- Is this a time to reconsider ARV?

Does it occur early?
If so- Why would we be concerned?

- < 45 years of age- early menopause
- < 40 years of age- premature menopause (less than 2 SD below the mean)
- In the absence of any pathological process- surgical, chemotherapy or radiation therapy
- associated with long-term **health risks** which may include **premature** death, cardiovascular disease, neurologic disease, osteoporosis, psychosexual dysfunction, and mood disorders

Average age of menopause for HIV positive women?

- Data is conflicting- no impact to 12% premature menopause- many reports of approximately 2 years earlier
- Early menopause is associated with substance use, low body weight, smoking , ethnicity
- Data is conflicting as to association to HIV viral load and CD4 cell count
- Why might it be earlier?
  - *Lymphocyte activation and inflammatory mediator impacting ovarian signalling*
  - *Impact of HIV or OI on ovaries and pituitary axis*

Andany Int J Woman Health, 2016: (8):1-22; Kang M, 2016; JCO : 23(1); Imai K, 2013: Obst Gyne Int, 2013

Étude sur la santé sexuelle et reproductive des femmes vivant avec le VIH au Canada

Canadian HIV Women's Sexual and Reproductive Health Cohort Study

- N=232
  - *53% white, 22% ACB, 19% indigenous*
  - *39% IDU*
  - *95% cART, 87% < 50/ml*
- Median age of menopause 48yr (IQR 43,51) – by self report
- 29% < 45 years

Andany, 7th women workshop, Seattle, 2017

Potential contributors to early onset of menopause in women with HIV

Immunosuppression

Lower CD4+ count has been associated with early menopause onset

Smoking

Menopause can occur up to 1–2 years earlier in smokers, compared with non-smokers

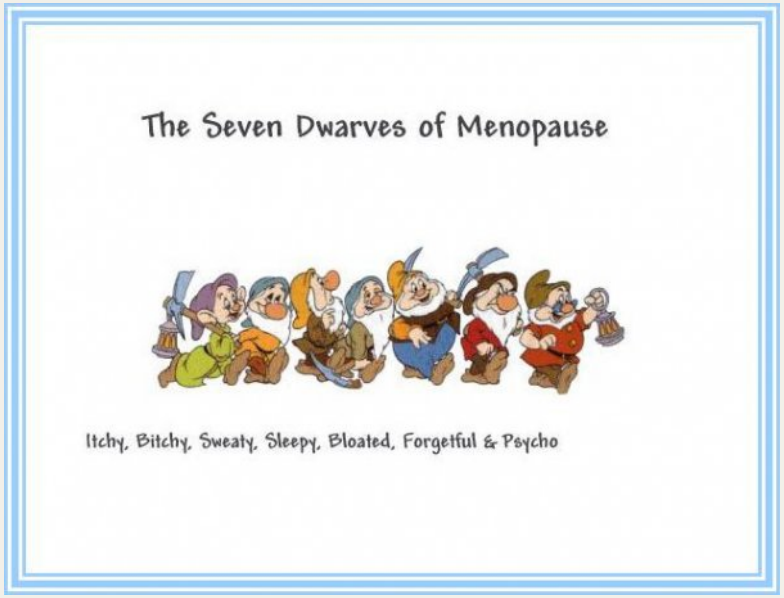
Socioeconomic status

Markers of low socioeconomic status (e.g. lower level of education, unemployment and poverty) have been associated with early menopause onset

de Pommerol (2011) Int J STD AIDS; Cooper (1999) Epidemiology; Luoto (1994) Am J Epidemiol; Gold (2001) Am J Epidemiol

Menopausal symptoms

- Hot flashes, sleep disturbance,
- Mood changes, vaginal dryness
- 85% of women in general population
- Median duration of 7.4 years
- Affected by: ethnicity, social economic status



- Negative impact on quality of life, performance at work and in relationships
- Data in WLWH mixed- no consistent association

Schnall R, Menopause 2018 25(7); 744-52

Do HIV+ women have increased menopausal symptoms?

- Being HIV+ increased the likelihood of experiencing menopausal symptoms by between 24-65% across studies
  - Higher prevalence of hot flushes, psychological complaints, reduced sexual interest, reduced concentration

- Increase in symptoms associated with
  - Socioeconomic status, depression, three or more negative life events

[1]Ferreira C, Pinto-Neto A et al. *Gynecol Endocrinol,* 2007; [2]Miller S, Santoro N. *Menopause* 2005

HIV and menopause in the UK

- N=140, WLWH > 45 years age
- Higher anxiety scores and severe depression compared to WLWH < 45 years
- Menopause Specific Quality in Life Questionnaire
  - *High reports of distressing symptoms*
  - *35/57 did not seek help for symptoms*

Sherr L, J Virus Erad, 2016; 2(4): 215-18.

Menopausal symptoms are associated with psychological distress in HIV+ women

Shema Tariq, Fiona Burns, Alexandra Rolland, Caroline Sabin, Lorraine Sherr, Richard Gilson (on behalf of the PRIME Study Group)

Institute for Global Health, University College London, UK

An analysis of cross-sectional data on 710 women recruited to the **PRIME Study** (Positive Transitions Through the Menopause), an observational study of WLWH aged 45-60 attending HIV clinics across England in 2016-2017.

Table 2: Association of severe somatic and urogenital symptoms with the following outcomes: (i) distress, (ii) anxiety, and (iii) depression (multivariable analyses)

	Adjusted odds ratio (95% CI)[a]	*p*-value
(i) Psychological distress		
Severe somatic symptoms	4.90 (2.71,8.88)	<0.001
Severe urogenital symptoms	2.66 (1.74,4.01)	<0.001
(ii) Anxiety		
Severe somatic symptoms	3.79 (2.27, 6.35)	<0.001
Severe urogenital symptoms	3.17 (2.03, 4.94)	<0.001
(iii) Depression		
Severe somatic symptoms	3.43 (2.04,5.76)	<0.001
Severe urogenital symptoms	2.90 (1.81,4.64)	<0.001

[a] adjusted for ethnicity, employment status, education, basic needs met, and high risk alcohol use

Abstract 1074,
CROI 2018

Association of HIV status with sexual function in women aged 45-60

Nasreen Toorabally[1], Catherine H Mercer[1], Kirstin Mitchell[2], Fiona Burns[1], Richard Gilson[1], Caroline Sabin[1], Shema Tariq[1] (on behalf of the PRIME Study Group)
[1]Institute for Global Health, University College London, UK; [2]Institute of Health & Wellbeing, University of Glasgow, UK

An analysis of cross-sectional data of sexually active women aged 45-60 from two national datasets from England:

- The **3rd National Survey of Sexual Attitudes & Lifestyles**, a national probability sample survey (HIV-negative women, N=1699)
- The **PRIME Study** (Positive Transitions Through the Menopause), a convenience survey of midlife women living with HIV (WLWH, N=336) attending HIV clinics across England.

TABLE 2: ASSOCIATIONS BETWEEN SEXUAL FUNCTION AND HIV STATUS (REFERENCE GROUP HIV-)

	Natsal-3 (HIV-) N=1228[a], 1677[b] n (%)	PRIME (HIV+) N=312 N (%)	Adjusted odds ratio[c] (95% CI)	*p*-value
Overall sexual function[d]				
Low sexual function	342 (20.4)	133 (42.6)	3.87 (2.35-6.38)	< .001
Lacked interest in sex	642 (38.3)	163 (52.2)	2.79 (1.50-5.16)	.001
Lacked enjoyment in sex	217 (13.1)	102 (32.7)	4.19 (2.08-8.41)	< .001
Felt anxious during sex	59 (3.5)	54 (17.3)	4.90 (2.55-9.42)	< .001
Physical pain due to sex	126 (7.5)	52 (16.7)	2.92 (1.91-4.46)	< .001
No arousal during sex	146 (8.7)	90 (28.8)	3.42 (1.98-5.91)	< .001
No orgasm/took long time to reach orgasm	25 (14.9)	97 (31.1)	2.92 (1.78-4.75)	< .001
Reached orgasm too quickly	40 (2.4)	23 (7.4)	1.79 (0.33-9.66)	.50
Vaginal dryness	288 (17.2)	86 (27.6)	2.27 (1.37-3.77)	.002
Experienced ≥1 problem	911 (54.3)	215 (68.9)	2.61 (1.54-4.45)	< .001

[a]Unweighted denominator; [b]Weighted denominator; [c]Adjusted for ethnicity, age, number of chronic conditions, depression and ongoing relationship status; [d]Using Natsal-SF

CROI abstract 1073, 2018

Does menopause negatively impact HIV?

- No studies have shown either an impact on CD4 cell count or response to cART

Imaj K, Obst Gyne Int, 2013

HIV– and HIV+ post-menopausal women.

Cellular markers of T cell activation, exhaustion, and sensecence

	HIV– women	HIV+ women	P value
	n = 13	n = 22	
T cell activation			
CD38+ HLA-DR+ CD4 (%)	1.69±0.95	3.21±1.87	**0.0313**
CD38+ HLA-DR+ CD8 (%)	2.08±1.39	10.17±13.26	**<0.0001**
Ki-67+ CD4 (%)	0.39±0.22	0.63±0.29	**0.0260**
Ki-67+ CD8 (%)	0.32±0.09	0.34±0.18	0.6913
T cell exhaustion			
PD-1+ CD4 (%)	13.36±6.81	21.99±11.80	**0.0321**
PD-1+ CD8 (%)	16.72±9.86	20.50±7.34	0.2177
T cell senescence			
CD28– CD57+ CD4 (%)	2.22±2.61	9.43±12.24	**0.0390**
CD28– CD57+ CD8 (%)	16.07±10.40	24.59±13.88	**0.0481**
CD127 CD4 (MFI)	3,457±901	2,737±890	**0.0368**
CD127 CD8 (MFI)	1,795±850	1,093±930	0.0512

Expression of activation (CD38, HLA-DR, Ki-67), exhaustion (PD-1) and senescence (CD28, CD57, CD127) markers was evaluated by flow cytometry in live CD4 and CD8 T cells. Cryopreserved PBMC were thawed and rested overnight before staining with ViViD and monoclonal antibodies and subsequent acquisition on a flow cytometer. Gating strategy for the phenotypic analysis of T cells was performed as follows: Lymphocytes were gated based on forward and side scatter, and gates for exclusion of singlets and dead cells (ViViD+ events) were drawn. Statistical differences between groups were analyzed by Student *t*-test. Significant P values are shown in bold.
doi:10.1371/journal.pone.0063804.t002

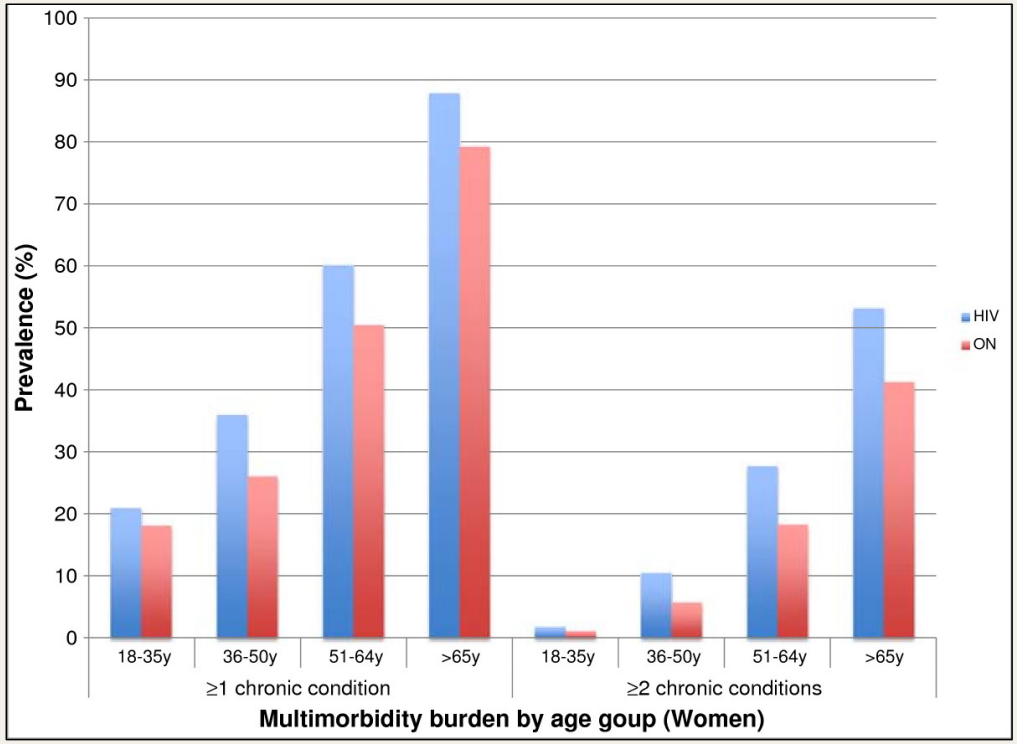
Soluble markers of immune activation and microbial translocation

	HIV- women	HIV+ women	P value
	n = 15	n = 27	
Monocyte/macrophage activation			
sCD14 (ng/ml)	1,537±253	2,113±426	**<0.0001**
sCD163 (ng/ml)	323±155	533±260	**0.0043**
T cell activation			
sCD25 (ng/ml)	387.3±151.2	590.1±425.6	**0.0423**
Cytokines			
IL-6 (pg/ml)	0.89±0.17	1.86±0.44	0.0728
IL-8 (pg/ml)	4.38±0.52	6.57±1.26	0.1012
IL-10 (pg/ml)	3.31±1.58	19.74±4.85	**0.0124**
TNFα (pg/ml)	7.02±1.43	9.58±1.23	0.1359
Microbial translocation			
LPS (pg/ml)	90.2±21.4	107.4±20.7	**0.0221**

Circulating levels of sCD14, sCD163 and sCD25 were measured in the plasma of 27 HIV+ post- women and 15 HIV- controls by ELISA. Plasma levels of cytokines were measured using a customized MILLIPLEX™ Cytokine Human Ultrasensitive magnetic bead panel (EMD Millipore). LPS levels were measured in plasma samples by the use of the Limulus amebocyte lysate chromogenic endpoint assay, as described in the Methods. Statistical differences between groups were analyzed by Student *t*-test. P values <0.05 are shown in bold.
doi:10.1371/journal.pone.0063804.t003

Alcaide ML et al. (2013) Immune Activation in HIV-Infected Aging Women on ARV—Implications for Age-Associated Comorbidities: A Cross-Sectional Pilot Study. PLoS ONE 8(5): e63804.

Comorbidity of HIV infected women in Ontario



Morbidity prevalence by age group among men and women with HIV versus the Ontario general population.

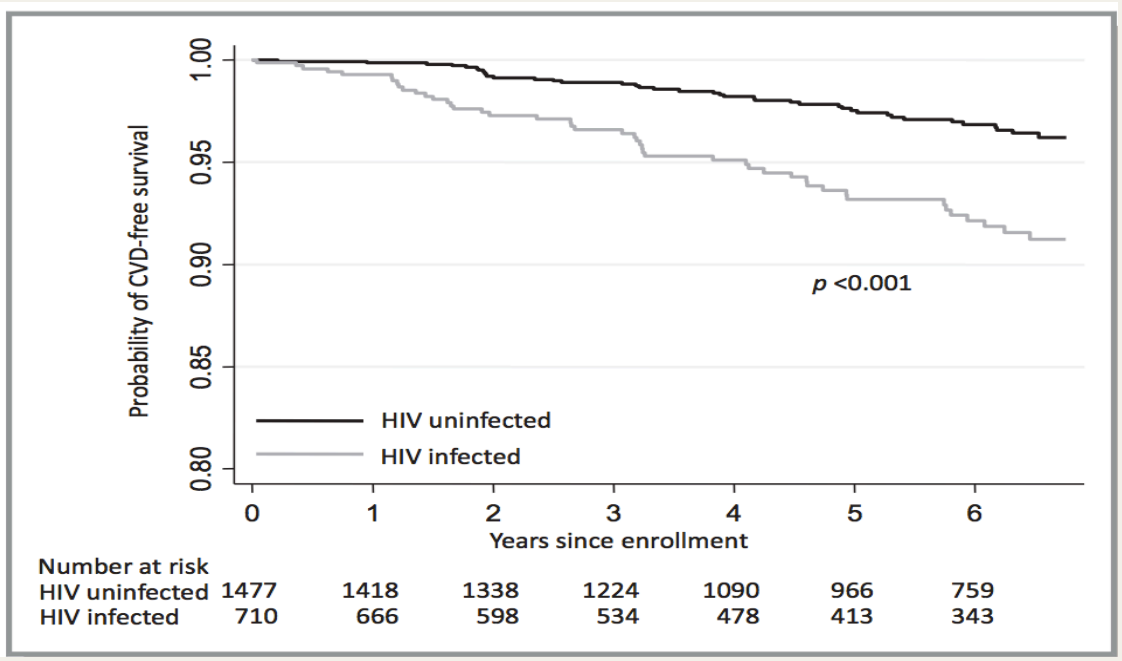
Kendall et al, BMC Public Health, 2014

Impact of Decreased Ovarian Reserve in HIV-infected women

- Undetectable Anti-Mullerian hormone levels
- 49 HIV+ and 25 HIV-
- Of the HIV+ those with undetectable AMH had a higher prevalence of coronary atherosclerotic plaque (52 vs 6%, $p<0.01$), noncalcified plaque (48 vs 6%)
- Associated with higher levels of sCD163 and MCP-1
- Holds when controlled for CVD risk

Looby et al, AIDS, 2016

HIV INFECTION AND CVD IN WOMEN: VETERANS AGING COHORT STUDY



Unadjusted Kaplan-Meier's curves showing CVD-free survival by HIV status.
CVD indicates cardiovascular disease.

N= 2187 women
(32% HIV+)

HIV women had an increased risk of CVD
HR 2.8, 95% CI 1.7, 4.6, p<0.001

Womack et al; JAHA 2014

HIV infection and women and ischemic stroke

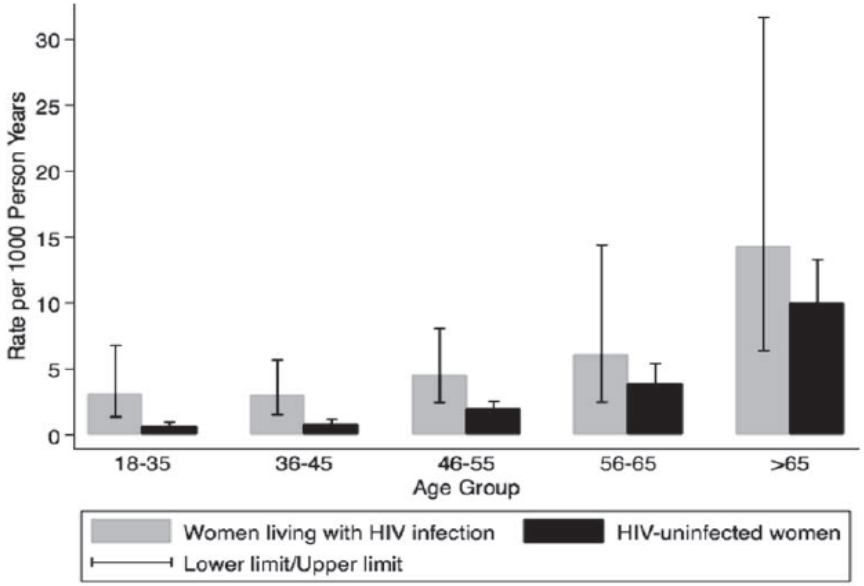
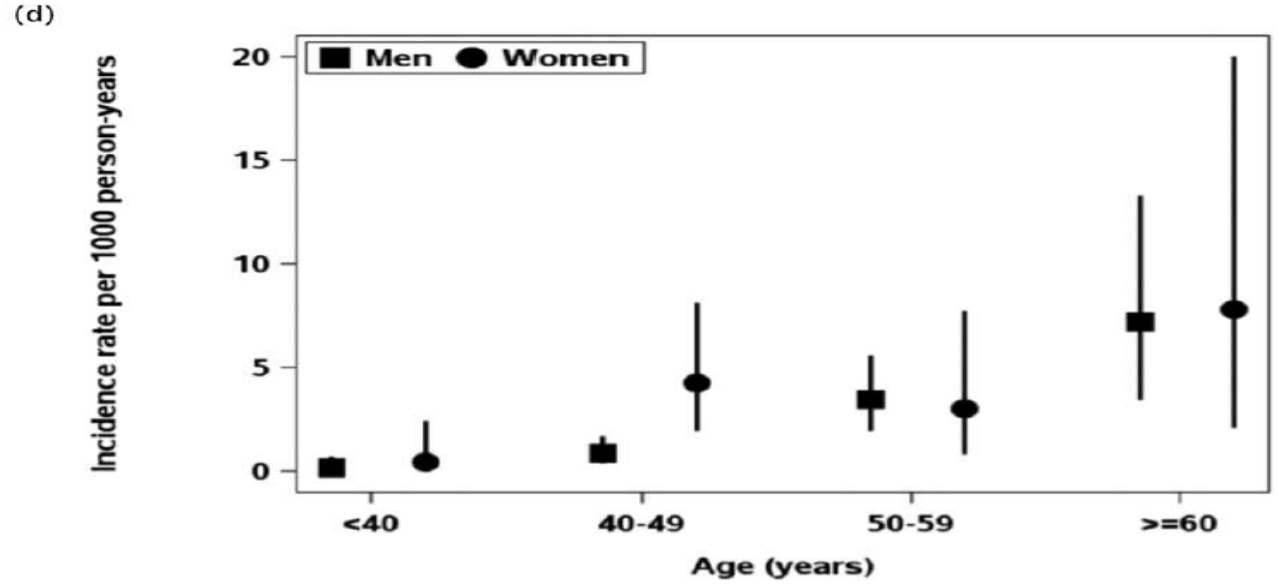


Fig. 1. Incidence rates for ischemic stroke in women from the Partners HIV cohort stratified by HIV status and age.

Chow et al, AIDS, 2018

Ischemic stroke in HIV infection



No. of strokes	M: 2	F: 1	M: 8	F: 9	M: 16	F: 4	M: 10	F: 4
Person-years	10,473	2,307	9,291	2,106	4,636	1,317	1,381	512
Rate (per 1000 PY)	**0.19** (0.02-0.69)	**0.43** (0.01-2.41)	**0.86** (0.37-1.70)	**4.27** (1.95-8.11)	**3.45** (1.97-5.60)	**3.04** (0.83-7.77)	**7.24** (3.47-13.31)	**7.81** (2.13-20.01)

Chow et al, AIDS, 2018

Bone Mineral Density and Osteoporosis

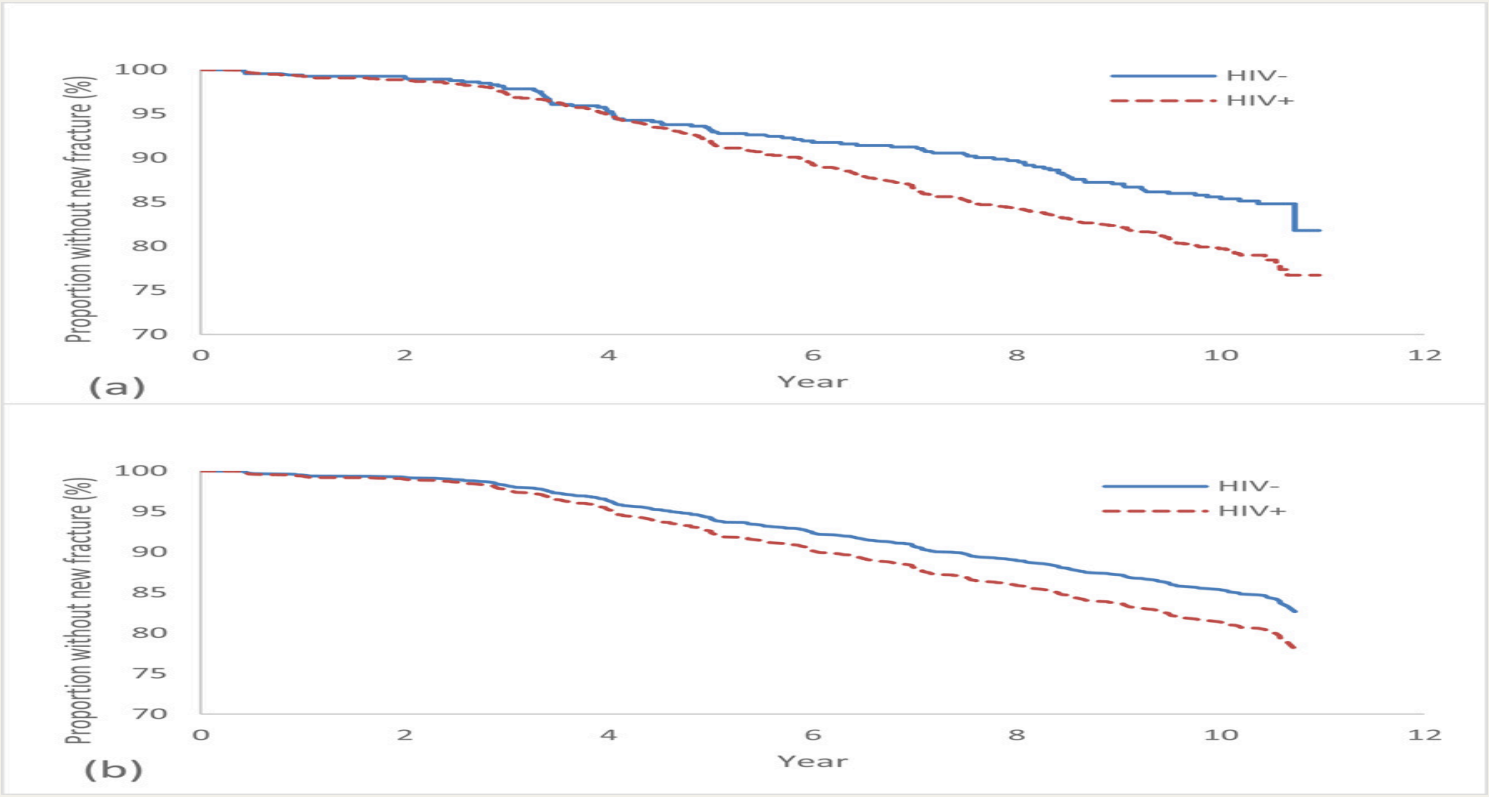
- Shown to be increased in HIV
- Risk factors include IVDU, cocaine, race
- Associated with ARV especially tenofovir and when combined with protease inhibitor

  - *Tenofovir-alafenamide may have less effect*

- NRTI sparing strategies show less BMD loss
- Associated with increased fracture risk especially in post menopausal women

Brown 2004, Tebas 2000, Brown, Bone 2006, Yin, 2005, Gallant 2017

Increased Fracture Incidence in Middle-Aged HIV-Infected and HIV-Uninfected Women: Updated Results From the Women's Interagency HIV Study



Risk factors in multivariate model: HIV, age, white race, cocaine, IVDU

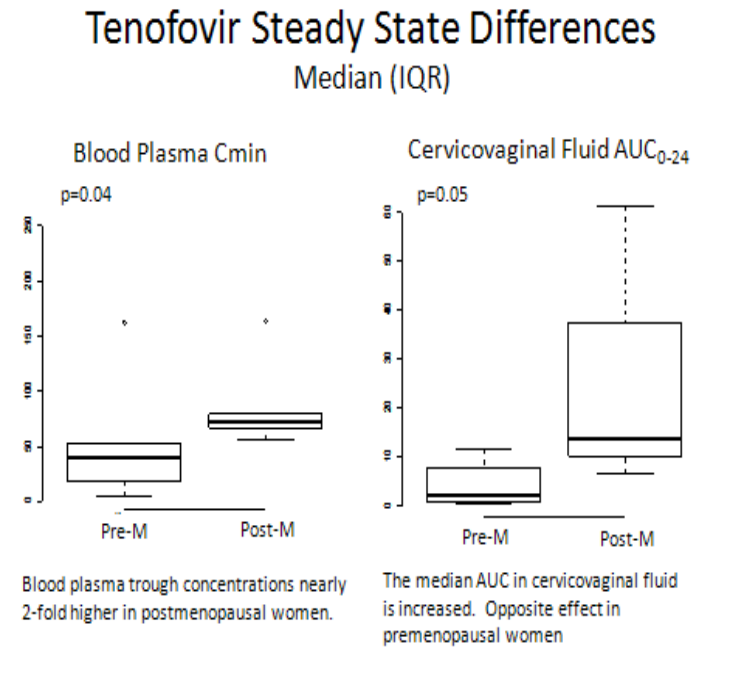
Sharma, et al. JAIDS Journal of Acquired Immune Deficiency Syndromes. 70(1):54-61, September 1, 2015.

Co-morbidity considerations for WLWH

- Cardiovascular disease
  - *increased risk in HIV and increased with premature menopause- no data on CVD outcomes*
- Bone mineral density and osteoporosis
  - *increased with age, HIV and ARV, few women in the TAF studies*
- Mental health
  - *a period of increased depression*
  - *WHIS study of 835 WLWH compared to a control group of 335 HIV negative women*
  - *no significance in difference in prevalence of depression between the two groups during menopause*
  - *odds increased in both groups in early peri-menopausal period*

Maki; Menopause 2012; 19(11):1215

Does menopause impact ARV drug concentrations?



Is it
- Aging
- Menopause or
- declining renal function?

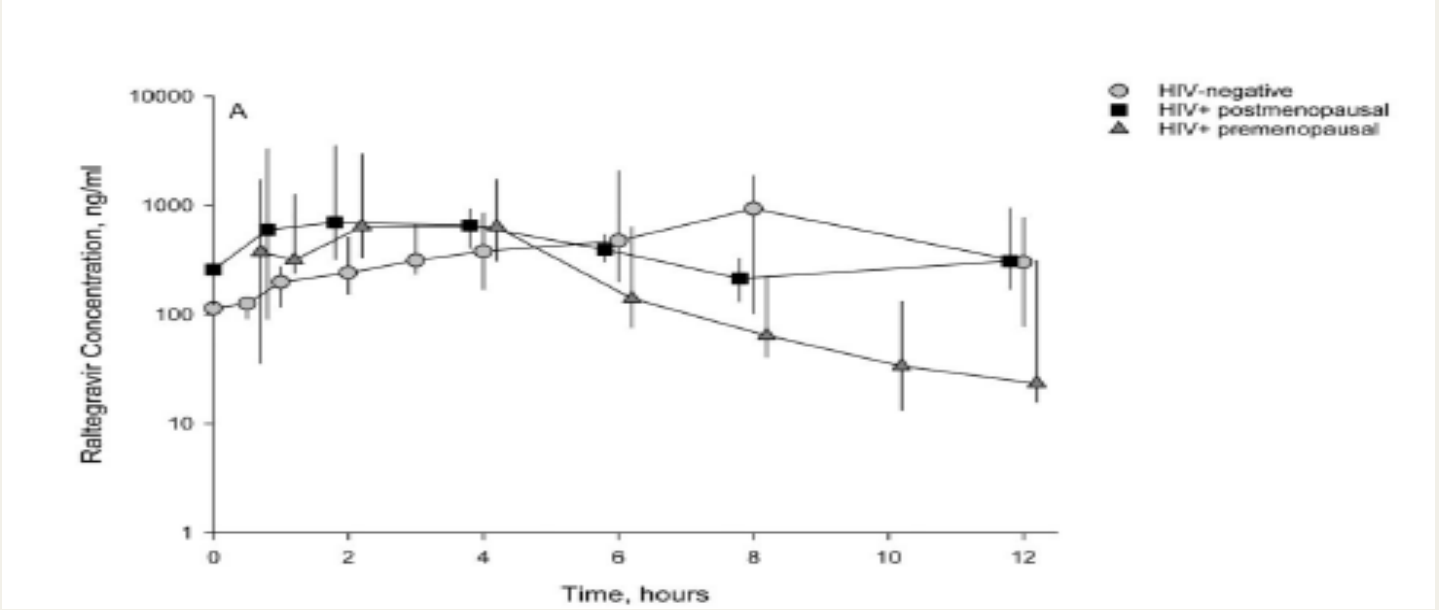
Patterson, CROI, 2011

Tenofovir
Women Interagency HIV Study (WIHS)

- N=105 HIV + women
- Mean age 41, 70% African American
- Persons with the highest baseline Tenofovir AUC tertile had significantly lower eGFR compared to those in lowest tertile
- By year 7 the difference widened

Baxi et al , AIDS, 2016

Raltegravir levels in the blood of HIV negative and HIV positive pre and post menopausal women



Cottrell et al, Antivir Ther; 2015 ; 20 (8): 795-803.

Managing the menopause in women with HIV

- Strategies to offset effects associated with menopause include:
  - Healthy lifestyle choices e.g. exercise and diet
  - Smoking cessation
  - Adherence to effective ART
  - Symptom management
  - Alternative therapies
  - Vaginal lubricants

- If these strategies don't help then Hormone replacement Therapy (HRT) can be considered

Monroe A. *BETA* 2007:39-441; 2. New York State Department of Health AIDS Institute. Medical Care for Menopausal and Older Women With HIV Infection.

The controversies around HRT

- Slight increase risk of stroke, DVT/PE, CVD and breast cancer
- No increase in endometrial cancer
- Reduced risk of colon cancer and hip fractures
- Improvement in vasomotor symptoms

- Poor compliance
- Adverse effects- breast soreness, weight gain, depression
- Cost
- Timing, active ingredient, route, duration

Chalouhi S, Post reproductive health 2017: 23(3): 128-131; Carrasquilla G, Plos Medicine, 2017: 14(11)

Hormone replacement therapy in HIV

- There are no studies in WLWH
- PI/r, cobicistat, and NNRTI may impact menopause hormone levels due to effects on cytochrome p450 enzyme activity
- need to titrate hormone levels to desired effects

Menopause hormonal therapy in HIV

- Studies in WLWH show rates of use of < 10%
- Concerns
  - *increasing pill burden and impacting adherence*
  - *increased risk of CVD (additive to smoking and dyslipidemia)*
  - *increased breast cancer risk*
  - *HIV has 2-10X increased risk of venous thromboembolism which could be additive to estrogen replacement (transdermal estrogen may confer less risk)*
- Recommendations follow that of the general population- if used at the lowest possible dose and for as short as possible

Conclusions

- The prevalence of HIV infection in older women is increased
- Differences in the age of onset, rate of menopausal symptoms and link to comorbidity relative to the general population is debated
- The peri-menopausal period is a time to reconsider cART and potential for additive comorbidity
- HCT may be useful to control vasomotor symptoms and decrease fracture risk but may have increased risks
- Drug interactions with cART must be considered