



HIV & Menopause

Women and HIV International
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E. Milu Kojic, MD

Brown University



Objectives

- Overview of growing old with HIV infection
 - Immune function
 - HAART toxicities
 - Metabolic complications
- Perimenopause and Menopause in HIV infected women
- Menopause Clinic data
- Clinical Recommendations for the menopausal woman

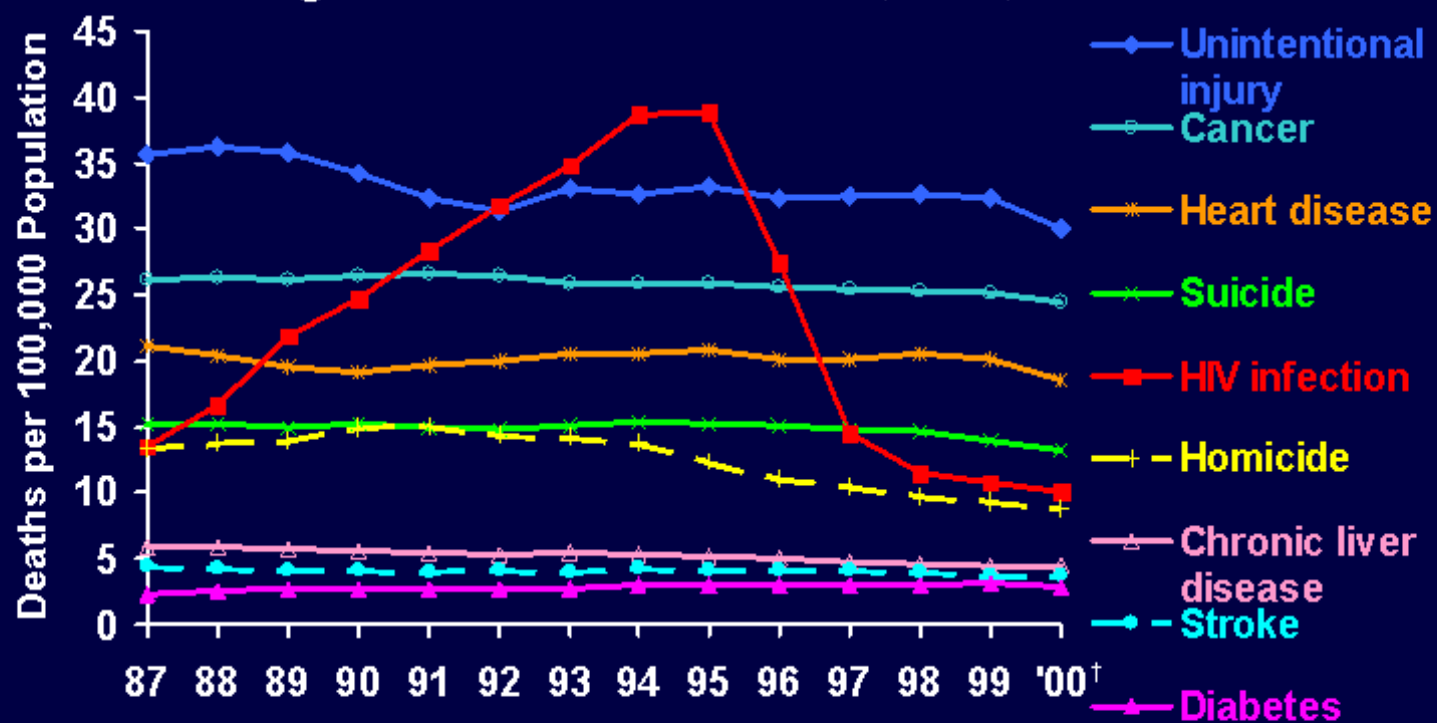
Epidemiology

- In the US life expectancy has increased with tripling of the percentage of women over 50 years of age in the last 100 years (Paoletti, Circulation 2003)
- Women represent 30% of new HIV infections in the USA (CDC)
- Antiretroviral therapy has resulted in dramatic reductions in morbidity and mortality among HIV infected individuals (Palella, NEJM 1998)
- In women over 50, the number of women with HIV tripled between 1993 and 1997

Number of people living with HIV	Total	37.8 million	[34.6–42.3 million]
	Adults	35.7 million	[32.7–39.8 million]
	Women	17 million	[15.8–18.8 million]
	Children <15 years	2.1 million	[1.9–2.5 million]
People newly infected with HIV in 2003	Total	4.8 million	[4.2–6.3 million]
	Adults	4.1 million	[3.6–5.6 million]
	Children <15 years	630 000	[570 000–740 000]
AIDS deaths in 2003	Total	2.9 million	[2.6–3.3 million]
	Adults	2.4 million	[2.2–2.7 million]
	Children <15 years	490 000	[440 000–580 000]

44.9%

Trends in Annual Rates of Death due to Leading Causes of Death among Persons 25-44 Years Old, USA, 1987-2000



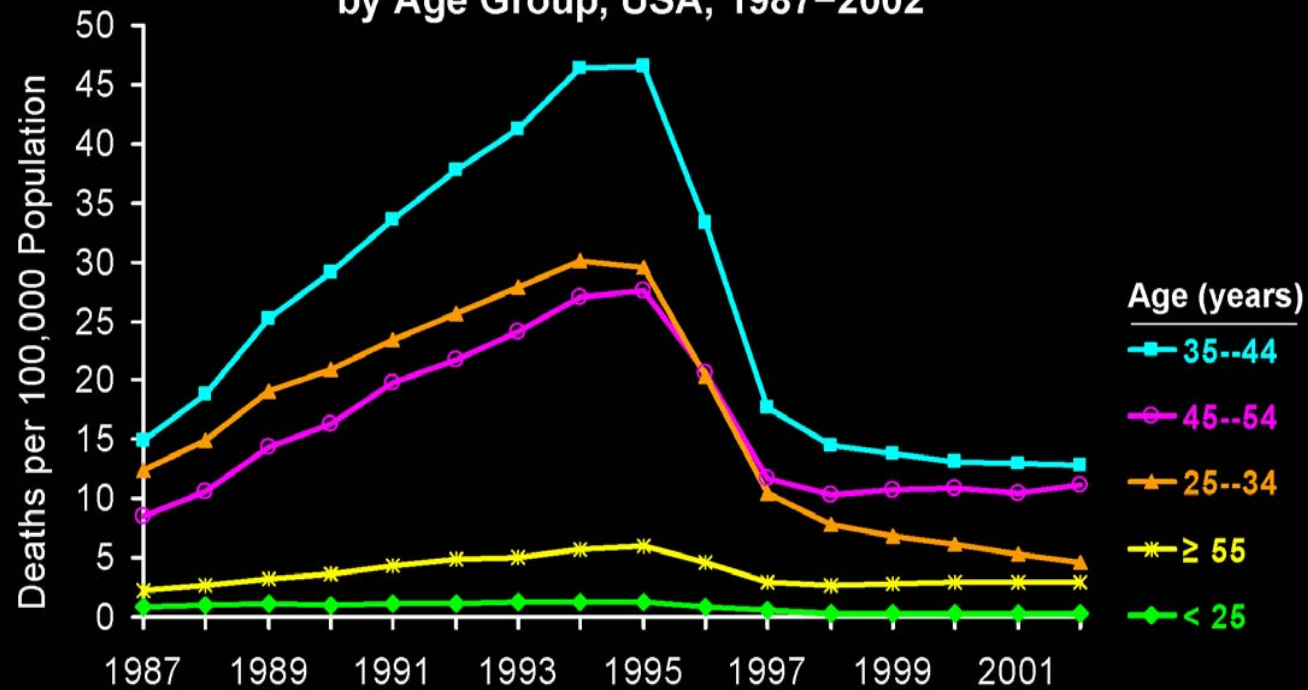
Note: For comparison with data for 1999-2000, data for 1987-1998 were modified to account for ICD-10 rules instead of ICD-9 rules.

Year

†Preliminary mortality data for 2000.



Trends in Annual Rates of Death due to HIV Disease by Age Group, USA, 1987–2002



Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.



Epidemiology

The population of HIV
infected women over the age
of 50 experiencing
menopause is growing
rapidly

Growing Old with HIV

- HIV-infected patients aged >50 now represent 10-13% of the HIV infected population in the U.S.
- 13% in Florida, 20% in Hawaii
- Older persons tend not to be perceived by MDs to be at risk for HIV
- Excluded from targeted testing
- Misdiagnosis is common
- El Sadr et al: 13/257 (5%) of blood samples from patients >60 y/o contained HIV antibodies
 - 9% women (7 out of 78)
 - 7% men (6 out of 92)

Age and Immune Function

- Parallel between age related immune down regulation and HIV related immune dysfunction
- When an older individual becomes infected with HIV, depletion of CD4 cells is more pronounced compared to younger patients; poorer immune response to ART
- May be related to thymus involution with age and decreased thymus productivity
- Pre-HAART era: >50 yrs more rapid progression to AIDS, poorer survival
- HAART era: older patients have delayed immune recovery, inverse relationship between age and maximum CD4 cell response

Age and Immune Function

- More recent studies (Tumberello et al, Fair Wellons et al) no age related differences in immune recovery, clinical outcome, greater proportion of older patients with undetectable plasma viral load, greater compliance with treatment
- Mortality (Perez et al) 253 pts. >50 yrs vs 535 younger patients: older patients not on therapy had twice the hazard rate for death than younger but after initiation of therapy, older patients had > 2 fold reduction in hazard for death and 72% reduction in mortality; after 3 mos there was no difference in survival rate between older and younger

HAART and Toxicity/Tolerability in Older Patients

- Older age is associated with decrease in renal and hepatic function
- Could lead to higher levels of ART and decreased tolerability
- Knobel et al: 64% of >60 yrs old had adverse events to protease inhibitors compared to 35% in younger group (P=.001)
- Many co-morbidities requiring medication may lead to drug-drug interactions
- NY City: >55 yrs, 89% had co-morbid conditions and 81% were taking non-HIV meds

HIV, Cardiovascular Disease, and Aging

- HIV related disorders: insulin metabolism, diabetes mellitus, lipodystrophy, dyslipidemia
- Considerable debate on premature cardiovascular and cerebrovascular disease and HIV and HAART
- Bozette et al: retrospective study of 36,766 HIV(+) patients on ART (1993-2001), 10% >55 yrs old; no increase in cardiovascular or cerebrovascular mortality attributed to ART
- DAD Study group: prospective observational cohort 23,468 HIV(+) (1999-2002), ART was independently associated with a 26% relative increase in rate of MI per year of exposure; older age was consistently associated with increased risk

HIV and Menopause

- In the general population menopause occurs between ages 48 and 55, with a median age of 51
- Do HIV infected women go through menopause earlier???

Perimenopause

- The years surrounding the last menstrual period
- When hormonal levels fluctuate accompanied by irregular menstrual periods
- When women have symptoms like hot flashes, night sweats, palpitations, depression, urinary incontinence, sleep disturbance, vaginal dryness

Menopause

- Defined as:
 - When the ovaries stop secreting estrogen because of follicular depletion
 - When the ovaries are surgically removed
 - When menstrual periods stop for at least 12 months
 - FSH >20 and/or estradiol <50

HIV and Perimenopause

- Suggestions that HIV was associated with menstrual disturbances, more likely to have long intervals between cycles (Shah, Obst Gyn 1994)
- A substudy of two large cohorts studies (HERS and WHIS), included 1075 women age 20-45 using menstrual calendars
 - Slight increase in very short cycles, no overall effect on amenorrhea, menstrual cycle length, or variability (Harlow, Cui-Uvin et al JAIDS 2000)

HIV and Perimenopause

- A survey of 101 women age ≥ 40 (ACTG)
(Clark et al, JAIDS 2000;23(1))
- Several symptoms of menopause are relatively prevalent among older HIV infected women
- No or few associations between these symptoms and age, menopausal status, CD4 counts, and HIV RNA levels

HIV and Menopause

- A study using stored serum samples from women age 20-42 who participated in ACTG studies (Clark et al, JID 2001;184)
 - 24 women had FSH levels tested
 - Menopause if FSH > 40 IU/mL
 - 2 of them, or 8% had early menopause, similar to the general population
 - Problem small number
- A survey of 101 women age ≥ 40 (ACTG), 52 had adequate menopausal information (Clark et al, JAIDS 2000;23(1))
 - 50% (26 women) were menopausal by FSH >35 IU/mL, >6 months of amenorrhea and over age 55
 - Mean age was 47 years (32-57), earlier age than the general population
 - Problem recall bias

Menopause age in HIV infected Women

- Several predictors of earlier age at menopause are common among HIV-infected women
 - tobacco smoking
 - low relative body weight
 - low socioeconomic status
 - depression
 - African American ethnicity
- a possible basis for HIV-infected women having menopause at an earlier age.

Menopause, Aging, and CD4 Cell Counts

- Advanced age (>50 years) is an independent prognostic factor for more rapid disease progression in untreated individuals
- Although some studies have shown that women have a lower initial viral load than men, there seem to be no gender-associated differences in CD4 counts
- Postmenopausal women have been shown to have a lower CD4 cell count than premenopausal women, 333 vs. 399 (van Bentem, AIDS 2002)

Bone Loss and HIV: Implications for Older Patients

- Tebas et al: patients on protease inhibitors reported to have higher prevalence of reduce bone mineral density
- Bruera et al: HIV infected patients regardless of ART exposure, no therapy, had higher prevalence of osteopenia and osteoporosis than HIV negative controls
- Grinspoon et al: 84 HIV infected women on HAART compared to HIV negative women of similar age, BMI, race: osteopenia in 64% HIV(+) and 30% HIV (-)

HIV, Menopause and Lipids

- HIV and/or its treatment elevate TG due to \uparrow VLDL and \downarrow TG clearance
- Lipodystrophy, or adipose tissue alteration associated with HAART
- More pronounced in women – 41.9% vs 29.5 (JAIDS 2003;34:58)
- Menopause associated with \uparrow cholesterol and \downarrow HDL once the protective effect of estrogen is lost

Glucose metabolism

- In men, some evidence of \uparrow insulin clearance in HIV infected (Endocr Review 1996;17:518)
- Protease inhibitors cause insulin resistance
- Lipodystrophy is associated with central obesity which is an independent risk factor for DM
- HRT use – inconsistent results on glucose tolerance.

HIV, Menopause, and Metabolic Changes

	HIV and/or treatment	Menopause ↓ estrogen
Bone	?osteopenia osteoporosis	osteopenia osteoporosis
Lipids	↑ TG	↑LDL ↓HDL
Glucose	HIV- ↓insulin clearance Tx- lipodystrophy	Glucose intolerance reduced with hormonal therapy

Clinical significance

- HIV-infected menopausal women have multiple, potentially additive factors that predispose them to metabolic complications.
- Studies need to confirm if they are clinically significant, translate into
 - Bone fractures
 - Mis
 - DM

Menopause Clinic at The Miriam Hospital Immunology Center

- Immunology Clinic:
 - about 1000 HIV infected men and women
 - 380 women
 - 104 women over the age of 45
- Menopause Clinic:
 - Opened Jan 2003
 - Plan is to evaluate menopausal and perimenopausal women
 - Determine prevalence
 - Collect data on HIV and therapy, menstrual history, bone and cardiovascular risk factors
 - Osteoporosis/osteopenia

Menopause Clinic at The Miriam Hospital Immunology Center

- Half day clinic, first Thursday of every month
- Detailed menstrual history
- PAP smears and mammography
- Menopause symptoms
- Osteoporosis risk factors
- Cardiovascular risk factors
- Medical history, including depression and substance use
- Medicines

Menopause/Perimenopause Clinic at The Miriam Hospital

Definitions used:

- Amenorrhea: no menses for at least 12 months
- Irregular menstrual periods
- Menopause: no menses for at least 12 months and FSH level over 25
- Perimenopause: irregular menstrual periods and rising FSH
- Hysterectomy
 - With oophorectomy: surgical menopause
 - Ovaries not removed: Menopause if FSH level over 25

Menopause Clinic at The Miriam Hospital Immunology Center

- Focused exam
- Check FSH, LH, TSH
- If in menopause, refer for a bone scan
- If not in menopause, follow up in one year
- Education regarding calcium intake
- Address any gynecological issues

Data Analysis

- Medical history, bloodwork, Pap smears, DEXA scan, and mammogram results were collected on 65 women.
- Descriptive statistical analysis was performed.

Results: Basic Information

Table 1. Demographic Information N = 65

n (%)

Mean Age (year)	49.9 (range 38-61)
Race/ethnicity: White	27 (42)
Black	22 (33)
Latino	15 (23)
Median CD4 Count (cells/uL)	413 (range 11-1399)
Mean Time after HIV Diagnosis (year)	11 (range 0-22)
Those on ARV	57 (88)
Those on PI-containing regimen	22 (34)
Those on ARV and PVL<75 copies/mL	45 (69)
Median Weight (lb)	149 (range 99-278)

Results: Summary of Medical History

Table 2. Summary of Medical History

Menopausal Symptoms N=46, n (%)		Cardiovascular Risk Factors N=46, n (%)		Osteoporosis Risk Factors N=46, n (%)	
Hot flashes	29 (63)	Inadequate exercise	21 (46)	Inadequate exercise	21 (46)
Night sweats	28 (61)	Smoking	17 (37)	Smoking	17 (37)
Difficulty sleeping	23 (50)	Prior CVD	17 (37)	Low Ca intake	17 (37)
Depression	21 (46)	Diabetes	5 (11)	White Race	17 (37)

Results: Risk Factors

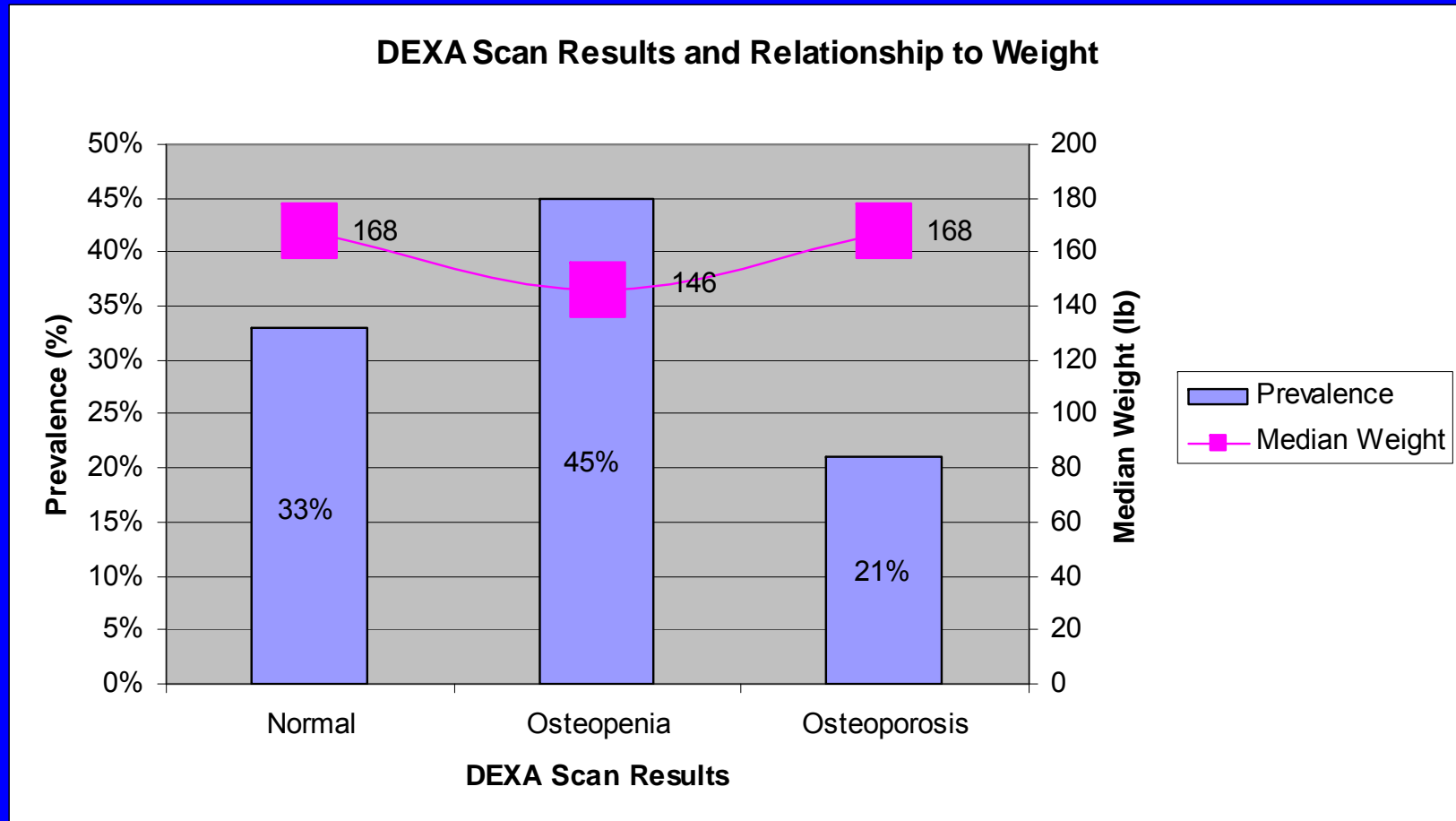
- Menstrual status: among women with complete history (n=46)
 - 37% (17/46) perimenopausal
 - 63% (29/46) menopausal
(including 7 with hysterectomies)
- 59% of women had ≥ 2 risk factors for osteoporosis.
- 13% (8/64) are current or recent users of methadone.
- 3 of the methadone users have normal DEXA scan results.
- 54% of women had ≥ 2 risk factors for cardiovascular disease.
- 15% (10/65) have weight > 200 lb

Results: DEXA Scan

- 42 women had DEXA scans within the last 2 years.
- 79% (15/19) of menopausal women had abnormal DEXA scan results.

Table 3. Bone Mineral Density			
	Perimenopausal and menopausal N=42,n(%)	Menopausal N=19, n(%)	Other Studies ⁴ (%)
Normal	14 (33)	4 (21)	36-62
Osteopenia	19 (45)	8 (42)	28-54
Osteoporosis	9 (21)	7 (37)	10

Results: Osteoporosis



Results: Lipids

Table 4. Lipid Panel

Unit: mg/dL	Mean N=63	HIV+ ♀ on Non-PI HAART	HIV+ ♀ on PI HAART	§Other studies on HIV+ ♀ ⁵	NHANES III ⁶
Total cholesterol	189.3	191.9	180.4	176	207.9
LDL	118.7	120.8	111.3	102	122.8
HDL	47.0	47.6	43.7	53	55.2
Total triglycerides	149.3	137.2	179.3	141	126.7

Results: Pap Smears

- 64 women had at least 1 Pap smear within the last 5 years.

Table 5. Pap Smears Results

	HIV Menopause Clinic N=64, n (%)	Miriam HIV Clinic ¹ 2006-2007 N=223, n (%)	HERS ^{2,3} (%)
Normal	44 (69)	150 (64.4)	44.7-61.9
ASCUS (%)	4 (6)	27 (11.6)	20.3
LGSIL (%)	13 (20)	49 (21)	16.1-28
HGSIL (%)	3 (5)	7 (3)	1.7-7

Results: Mammograms

- 51 women have had mammograms.
78%(40/55) Normal
- Others reported benign findings: include microcalcifications, fibroadenoma, lipoma

Discussion

- Metabolic complications of HIV and HAART are significant.
- Weight/high BMI does not seem to be related to less osteopenia/osteoporosis in this cohort.
- Lack of matched controls – effect of HIV, age, menstrual status, race, BMI, smoking, substance abuse

Conclusions

- HIV-infected perimenopausal and menopausal women have high prevalence of osteopenia/osteoporosis (66%) as well as risk factors for cardiovascular disease.
- There is a great need to evaluate the interplay between HIV infection, HAART, and menopause.