Meeting report

1st International Workshop on HIV & Aging

4 - 5 October 2010, Baltimore

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Report

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Impact of Aging on HIV Infection and Non-AIDS Diseases

Report from the 1st International Workshop on HIV & Aging, 4-5 October 2010, Baltimore

Written by Mark Mascolini

When triple antiretroviral therapy turned HIV infection into a chronic disease, few HIV clinicians figured they would soon need to refresh their understanding of Apo-A1, hemoglobin A1c, osteoclasts, osteoblasts, and renal tubule thickets. But when people with HIV started surviving into their late 40s, 50s, and 60s, simple clinical observation soon disclosed an unusually high propensity to heart disease, diabetes, liver failure, kidney failure, broken bones, and a conflux of "non-AIDS" cancers.[1]

Not until the 1st International Workshop on HIV and Aging, however, have HIV researchers and clinicians gathered to focus solely on pivotal questions about why AIDS survivors now often face early-onset atherosclerosis, osteopenia, and neurocognitive impairment. To address those questions, more than 160 researchers and representative of industry, government, and the HIV community gathered to consider 21 oral reports and a similar number of poster presentations selected by a scientific committee chaired by Charles Flexner (Johns Hopkins University, Baltimore) and Scott Letendre (University of California, San Diego).

In a series of invited lectures, 11 experts offered a broad perspective on current controversies and research on aging in people with and without HIV infection. Reviewing physiological pathways to frailty, Luigi Ferruci (National Institute on Aging) defined the aging phenotype as "highly variable age-associated changes in organs, tissues, and cells that diminish functional reserve and confer vulnerability to stressors and/or disease."[2] He noted that age is the strongest risk factor for any chronic disease, and he proposed that no variable predicts disability in aging better than inflammation. For example serum levels of interleukin 6 predicted incident disability in a large case-control study.[3]

Russell Tracy (University of Vermont) handled the hot topic of inflammation and premature aging in people with HIV infection.[4] Inflammation has assumed a central role in HIV-related aging research because epidemiologic evidence indicates that "essentially all chronic diseases of old age" are associated with inflammation markers. Yet Tracy stressed that in well-controlled HIV infection, markers of inflammation do not reach extraordinarily high levels and, in fact, often remain in the range that would be considered normal. He proposed four points to remember when considering the impact of inflammation in HIV-positive people:

- Despite being an immunodeficiency disease, HIV infection is an inflammatory disorder.
- Inflammation is associated with risk of death from all causes, not just AIDS-related death.
- Inflammation is associated with decreased lymphoid organ function (chronic low-level "wound repair").
- Comorbidities are critical to understanding biomarkers and risk factors in HIV infection and AIDS.

Tracy proposed the following working hypothesis of aging: With age, quality remodeling gives way to poor remodeling, which is driven by evolutionary biology and has many mechanisms, but virtually all mechanisms are related to inflammation. Exposure to agents like HIV accelerates this overall process through generalized increases in inflammation mediators. Ultimately, unless dysfunction of a single organ prevails, homeostasis leads to multiorgan failure and death. Like other chronic diseases, Tracy noted, HIV increases inflammatory stimulation. What is unique about HIV is that is also dysregulates the adaptive immune system. The result is a more accurate mimicry of aging.

Steven Deeks (University of California, San Francisco)[5] cited data suggesting that more than 80% of patients taking effective antiretroviral therapy have persistent low-level viremia.[6] His group showed that, despite long-term antiretroviral therapy, levels of immunosenescent CD8 cells are higher in HIV-positive people than in age-matched controls.[7] Several age-associated diseases also appear to be more common in people with treated HIV infection than in age-matched uninfected people, including cardiovascular disease, left ventricular dysfunction, non-AIDS cancers, osteopenia and bone fracture, liver
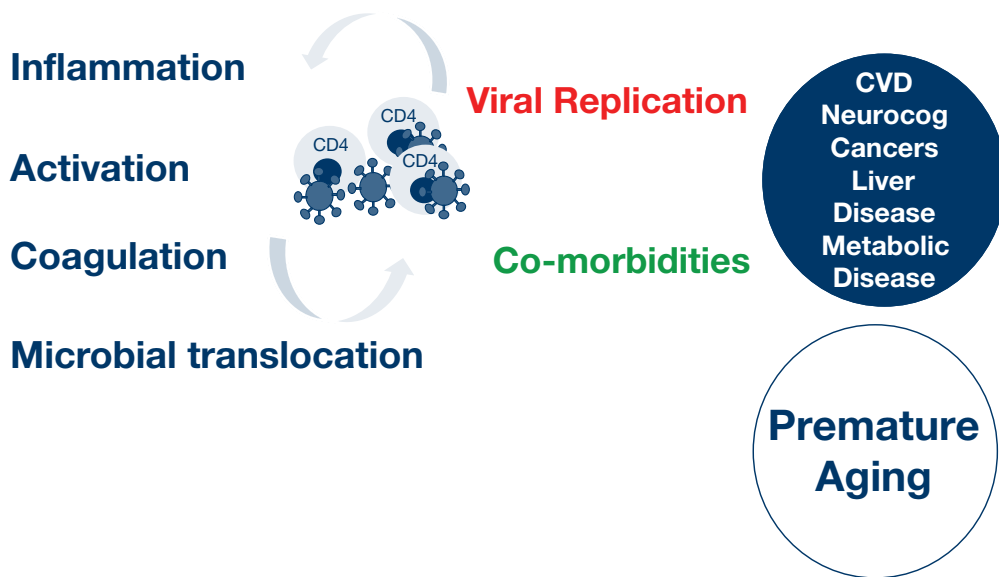
Figure 1. Even in well-controlled HIV infection, ongoing inflammation and T-cell activation may conspire with other variables to allow premature development of numerous non-AIDS diseases. (Slide adapted by Dr Seema Desai, Rush University, Chicago[12])

failure, kidney failure, cognitive decline, and frailty. A simple model for what is happening, Deeks proposed, is that persistent HIV replication/production during therapy causes inflammation/immunosenescence, and these processes in turn contribute to non-AIDS diseases.

Yet Deeks argued "there is no clear evidence that low-level viremia causes inflammation and non-AIDS morbidity."[8] In contrast, he maintained, cytomegalovirus (CMV) "almost certainly contributes to excess inflammation" in people with HIV infection. Other possible contributors include microbial translocation, tissue fibrosis, loss of T-regulatory cells, and thymic dysfunction. However, Deeks believes "extensive data indicate that inflammation during effective antiretroviral therapy predicts disease."

Joseph Margolick (Johns Hopkins Bloomberg School of Public Health) reviewed data from the Multicenter AIDS Cohort Study (MACS) indicating an association between frailty and untreated HIV infection, an association that persists after suppression of viral replication.[9-11] This work showed an association between HIV infection and more than a 10-year earlier-than-normal occurrence of a phenotype related to frailty. Margolick called for longitudinal studies "to evaluate mechanisms, prognostic impact, treatment, and prevention of frailty, and the role of antiretrovirals," adding that proper comparison groups will be essential in such studies.

Reviewing the immunology of aging, Alan Landay (Rush University Medical Center) proposed that research on immunologic and physiologic alterations, along with comorbidities, in people with HIV suggest that advanced aging occurs in HIV disease (Figure 1).[12] That proposal rests on the hypothesis that repeated antigen-driven stimulation in HIV infection results in differentiation and enrichment of a T-cell population with shortened telomeres and declining immune function, in other words, immunosenescence. This process occurs despite effective antiretroviral therapy[13] and may be hastened in older HIV-positive people, in whom T-cell turnover is faster than in younger counterparts. Landay stressed that HIV is not the only driver of T-cell turnover in HIV-positive people, who are often coinfected with other viruses, notably including CMV, hepatitis B virus (HBV), and hepatitis C virus (HCV).

Douglas Wallace (University of Pennsylvania) began his discussion of the role of mitochondria in aging by noting that life depends not only on a collection of organs and anatomical units, but also upon the energy that flows through the body.[14] Mitochondria, which are governed by non-Mendelian genetics, control this flow. HIV is toxic to mitochondria, Wallace observed, but the impact of the retrovirus on mitochondria remains poorly studied. His research focuses in part on how HIV-induced mitochondrial toxicity drives inflammation, the pathologic process that figures prominently in all models of accelerated aging with HIV infection. Wallace believes both ancient adaptive polymorphisms in mitochondrial DNA and recent deleterious mutations

inhibit oxidative phosphorylation, a central mechanism in mitochondrial dysfunction and, as a result, aging. From the FDA Office of Clinical Pharmacology, Darrell Abernethy addressed drug side effects that mimic aging.[15] Renal elimination of drugs decreases sharply with aging, he noted. Although less is known about the impact of aging on other elimination pathways, elimination via cytochrome P450 pathways (critical in metabolism of many antiretrovirals), may also decrease with aging. Older people have increased sensitivity to sedatives, anticholinergics, and antidopaminergics, decreased sensitivity to beta-adrenergic agents and angiotensin blockers, and impaired baroreflex and endothelial function. He listed four antiretroviral side effects that may mimic aging:

- Lipoatrophy/lipodystrophy
- Hyperlipidemia leading to cardiovascular disease
- Osteopenia/osteoporosis (?)
- Frailty syndrome (?)

Abernethy reviewed evidence showing that an increasing drug burden index is independently associated with functional impairment in older adults in the general population. Results from interventional studies are needed to assess whether reducing the drug burden index is feasible and whether changes in that index affect function in older adults. He proposed that optimizing use of drugs with anticholinergic and sedative effects with the help of evidence-based tools such as the drug burden index may reduce functional decline and disability among older adults. Three Aging Workshop studies reviewed below assessed polypathology and polypharmacy in aging HIV populations.

Janice Schwartz (University of California, San Francisco) analyzed similar issues from a different perspective—the effect of aging on pharmacology.[16] She stressed that age is only one of many factors that may affect pharmacokinetics and pharmacodynamics, which may also be altered by genetics, gender, race, disease, and the environment. Aging may affect drug volume distribution by changing at least four body composition components:

- Total body water decreases.
- Intravascular volume decreases.
- Muscle mass decreases.
- Bone density decreases.

Research has established that aging affects pharmacodynamics through several processes, Schwartz noted: (1) blunted reflex responses, (2) decreased receptor content/responses (including beta-adrenergic and dopaminergic receptors), (3) decreased reserves of all organs and systems, and (4)

increased bleeding response to anticoagulants. She proposed two clinical messages from research on aging and pharmacology: use as few medications as possible and anticipate interactions. She also urged clinicians to estimate glomerular filtration rate before dosing renally eliminated drugs.

Impact of Age on HIV presentation and response

CD4 count at entry into HIV care lower in older people

In the North-American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which combines data from 14 US and Canadian HIV cohorts, median age at presentation for HIV care rose significantly from 40 to 43 since 1997 (P < 0.01).[17] In a 12,000-person NA-ACCORD analysis published around the time of the Aging Workshop,[18] every 10 years of age lowered the chance of a good CD4 response to initial therapy with a boosted protease inhibitor (PI) or a nonnucleoside (NNRTI). Compared with people who started their first antiretroviral combination when 18 to 29 years old, chances of gaining 100 cells/µL waned in each older age group by the following adjusted hazard odds ratio (aHOR) and 95% confidence intervals (CI):

- 30 to 39: aHOR 0.92, 95% CI 0.85 to 1.00
- 40 to 49: aHOR 0.85, 95% CI 0.78 to 0.92
- 50 to 59: aHOR 0.82, 95% CI 0.74 to 0.90
- 60 or older: aHOR 0.74, 95% CI 0.65 to 0.85

In an NA-ACCORD study presented at the Aging Workshop, HIV-positive people 50 and older had consistently lower CD4 counts than younger people when entering care from 1997 through 2007.[19] Although median CD4 count at presentation rose in both the older and younger groups over the study period, in 2007 the 50-and-older group had not reached the median CD4 entry point younger people were at in 1997.

Older people start with fewer CD4s and gain fewer during trials

Analysis of the GlaxoSmithKline antiretroviral trials database showed that people under 50 years old when enrolling in trials had higher CD4 counts than older people, and the younger group gained more CD4 cells through 48 weeks of treatment.20 The younger group also enrolled in the trials with a higher (better) CD4/CD8 ratio, but improvements in that ratio were similar in the younger and older groups through week 48.

Decreasing potential to make new T cells with advancing age is a long-appreciated phenomenon.

In research focused on people with HIV infection, a 108-person cohort study associated older age with a higher likelihood of failing to gain at least 50 CD4 cells/mm3 during the first year of suppressive antiretroviral therapy.[21] A 423-person cohort study in San Francisco associated younger age with greater CD4-cell gains in the first 4 years of antiretroviral therapy.[22]

James Demarest and ViiV Healthcare/GlaxoSmith Kline colleagues assessed the impact of age not only on CD4 count, but also on CD8 count, CD4 and CD8 percent, and CD4/CD8 ratio upon entry into antiretroviral trials and after 48 weeks of treatment.[20] All study participants were antiretroviral naive at study entry, all began at least triple antiretroviral therapy, and all had matched baseline and 48-week efficacy data.

The study group included 6439 adults, 655 (10%) of them 50 or older when the trial began (mean 56 years) and 5774 of them 18 to 49 years old (mean 35 years). The older and younger groups were similar in gender (82% and 79% men) but differed in median pretreatment CD4 and CD8 measures:

- Median CD4 count:
  246 older vs 288 younger (P < 0.0001)
- Median CD4 percent:
  17% older vs 19% younger (not significant)
- Median CD8 count:
  800 older vs 825 younger (not significant)
- Median CD8 percent:
  62% older vs 58% younger (not significant)
- CD4/CD8 ratio:
  0.27 older versus 0.33 younger (P < 0.0001)

Across age-group deciles, median CD4 count change from baseline to week 48 tended to be smaller in the older groups (about 160 cells/mm3 in 39-to-40-year-olds, 41-to-44-year-olds, and 45-to-49-year-olds; and under 160 cells/mm3 in 50-to-78-year olds) than in younger groups (about 180 cells/mm3 in 18-to-26-year-olds and 26-to-28-year-olds and always above 160 cells/mm3 in the next four age groups, spanning 29 to 38 years of age). Comparing people 50 or older with younger trial participants, the investigators found a significantly greater CD4 gain in the younger group (173 versus 153 cells/mm3, P = 0.0037). The change in CD4/CD8 ratio through 48 weeks did not differ significantly between the older and younger groups (+0.2 versus +0.3).

As in all analyses of clinical trial participants, the results may not reflect a broader population of HIV-infected people who do not enter trials. Trial participants are usually considered to be more aggressive in managing their health and to have greater access to care. Demarest noted that it could prove useful to analyze T-cell changes not only by age, but also by starting values in younger and older people. Still, the results offer broad confirmation that older infected people may have more advanced HIV infection when they enter care and that they may have a slower or less complete immunologic response to antiretrovirals, at least in the first year of treatment. A study like this cannot determine whether older people had lower baseline CD4 counts because they got diagnosed with HIV later in the course of their illness or whether older age itself accounted for lower CD4 count.

CD4 response better in older patients starting maraviroc versus comparators

Older people entering randomized trials of maraviroc had lower CD4 counts than younger people, and the older group gained fewer CD4 cells during the trials.[23] But older people randomized to maraviroc gained significantly more CD4 cells through 24 weeks than did people randomized to comparator agents in these antiretroviral-naive and experienced trial populations.

Throughout development of maraviroc, a CCR5 antagonist, researchers noted a better CD4 response in the maraviroc arms, even after statistical adjustment for other factors affecting CD4 gains.[24,25] An attempt to exploit this apparently superior CD4-boosting potential failed in a pilot study of maraviroc added to a suppressive regimen that yielded an inadequate CD4 response.[26] Two meta-analyses of CD4 responses in clinical trials disagreed on whether CCR5 antagonists hold an advantage over other antiretroviral classes.[27,28] These meta-analyses were not able to adjust for factors predicting CD4 cell restoration.

How older age affects CD4-cell gains in people starting maraviroc versus other regimens had not been addressed until this analysis of CD4 and CD8 changes in the two MOTIVATE trials (which enrolled treatment-experienced patients), MERIT, and study 1078 (both of which enrolled treatment-naive people). Hernan Valdez (Pfizer) and colleagues from maraviroc trials analyzed T-cell changes at baseline and through 24 weeks, using a last-observation-carried-forward method for people who stopped treatment before week 24.

The investigators divided trial participants into age quartiles of 17 to 36 years (297 on maraviroc, 236 in comparator arms), 37 to 42 years (309 on maraviroc, 152 in comparator arms), 43 to 48 years (306 on maraviroc, 125 in comparator arms), and 49 to 77

years (347 on maraviroc, 116 in comparator arms). About 80% of study participants were men. One third of maraviroc recipients were antiretroviral-naive and two thirds experienced. These proportions were precisely reversed in the comparator arms. The study groups included 699 maraviroc recipients (55%) who attained a viral load below 50 copies/mL at week 24 and 393 (62%) who reached that mark in the comparator arms.

Study participants in the youngest age quartile had higher baseline CD4 counts (241 cells/mm3 in maraviroc arms and 270 cells/mm3 in comparator arms) when compared with the second age quartile (182 and 238 cells/mm3), the third quartile (178 and 221 cells/mm3), and the fourth quartile (207 and 221 cells/mm3). The youngest quartile also had the highest baseline CD4/CD8 ratio in both the maraviroc and comparator arms (0.275 and 0.325) versus the second quartile (0.205 and 0.245), the third quartile (0.195 and 0.250), and the fourth quartile (0.210 and 0.215).

After 24 weeks of treatment, CD4 gains were greater in patients taking maraviroc than in those taking other regimens in every age quartile (Table 1). But the difference between the maraviroc arm and the comparator arm was statistically significant only in the two oldest quartiles (Table 1). Among virologic responders, the CD4 increase with maraviroc versus comparator regimens was statistically significant only in the youngest quartile (152 versus 116.5 cells/mm3, P < 0.05).

CD8-cell counts rose in maraviroc recipients in every age quartile, while falling in patients taking comparator regimens in every quartile. Valdez proposed that this finding reflects redistribution of CD8 cells from cellular compartments to the peripheral circulation. After week 24, he noted, CD8-cell levels typically fall in people taking maraviroc. Because of the CD8-cell gains in maraviroc arms, the week-24 increase in CD4/CD8 ratio was significantly less with maraviroc in the three younger age quartiles (0.120 versus 0.180 in quartile 1, 0.060 versus 0.125 in quartile 2, and 0.045 versus 0.080 in quartile 3, P < 0.05 for all). For study participants in the oldest quartile (49 to 77 years), the improvement in CD4/CD8 ratio was equivalent with maraviroc and comparator regimens (0.055 versus 0.058). Notably, the improvement in the CD4/CD8 ratio tended to be greater in the younger quartiles than in the older quartiles regardless of treatment assignment.

Linear regression analysis indicated that five variables predicted a greater 48-week CD4 response: use of maraviroc, younger age quartile, higher baseline CD4 count, being antiretroviral naive, and achieving a week-24 viral load below 50 copies/mL. This analysis showed no significant interaction between age and maraviroc use.

Age and Neurologic outcomes with HIV

In an invited lecture, Avindra Nath (Johns Hopkins University) explored pathophysiologic mechanisms behind age-related neurocognitive changes in people with HIV infection.[29] He proposed that the HIV Tat protein drives neuropathology in infected people. Tat continues to be formed in people responding well to antiretroviral therapy because current antiretrovirals do not target Tat.

HIV Tat inhibits the amyloid-degrading enzyme neprilysin.[30] Possibly as a result, amyloid plaques (a

Table 1. Week-24 Response by Age Group in Four Maraviroc Trials

Age quartile	Median CD4 gain at 24 weeks	
	Maraviroc regimens	Comparator regimens
1 (17 to 36 years)	133.5 (n = 207)	111.0 (n = 236)
2 (37 to 42 years)	106.0 (n = 309)	96.5 (n = 152)
3 (43 to 48 years)	85.8* (n = 306)	56.0 (n = 125)
4 (49 to 77 years)	90.5* (n = 347)	59.3 (n = 116)

*P < 0.05 versus comparator. Antiretroviral-naive or experienced patients randomized to maraviroc in four trials gained more CD4 cells through 24 weeks of treatment than patients in comparator arms, but the difference between maraviroc and comparator regimens was statistically significant only in the two older quartiles. (Source: Hernan Valdez, Pfizer, New York.[23])

hallmark of Alzheimer's disease) are more frequent in people with HIV infection than in HIV-negative controls.[31] However, unlike plaques in patients with Alzheimer's disease, amyloid plaques in HIV patients are diffuse and do not have tangles.[32] Tat also mediates T-cell activation, Nath noted, and chronic T-cell activation has been documented in cerebrospinal fluid despite antiretroviral therapy.[33] Activated T cells are neurotoxic. In a workshop discussion following his presentation, Nath agreed that activating T cells latently infected with HIV in an attempt to eradicate the virus could release Tat and other mediators of neurotoxicity that could have deleterious clinical consequences.

Worse neuropsychological function with family history of dementia in people with HIV

In the general population, neurodegenerative diseases are at least partially inherited, as evidenced by a higher risk of dementia in people with a family history of dementia. For the first time, a study of people with HIV infection indicates that those with a family history of dementia have worse neuropsychological function as determined by standard tests.[34] Age did not interact with family history to increase the risk of worse neuropsychological function in this analysis. Whether HIV-associated dementia develops more frequently in people with a family history of dementia remains to be determined.

Incidence of HIV-associated dementia had decreased since the advent of triple antiretroviral therapy,

but prevalence of HIV-associated neurocognitive disorders (HAND) remains stable in the current treatment era. In addition to HIV-associated dementia, HAND includes asymptomatic neuropsychological impairment and mild neurocognitive disorder. HAND is more prevalent in older than younger people with HIV infection.[35,36]

This study by David J. Moore and CHARTER Group colleagues set out to address three questions: Does a family history of dementia raise the risk of neuropsychological impairment in people with HIV? If it does, which neuropsychological domains are affected? And does the effect of a family history of dementia differ between HIV-infected people under 40 years old and those 50 or older?

The study group consisted of 1104 CHARTER cohort members who reported whether a first- or second-degree relative had dementia. All study participants completed the CHARTER neuropsychological battery, which assesses verbal fluency, executive functioning, speed of information processing, learning, recall, working memory, and motor skills. The researchers converted raw test scores into T scores adjusted for age, gender, and education, then summarized these T score into a 0- to 5-point deficit scale to create a global deficit score and a score for each neuropsychological domain. A global score of 0.5 or greater indicated impairment.

The 190 people (17%) who reported a family history of dementia had a higher proportion of Caucasians than the 914 people who did not have a family history

*p<0.05; Cohen's d = .18; Standard error bars represent 95% confidence intervals

Worse NP performance in FHD group consistent across age ranges
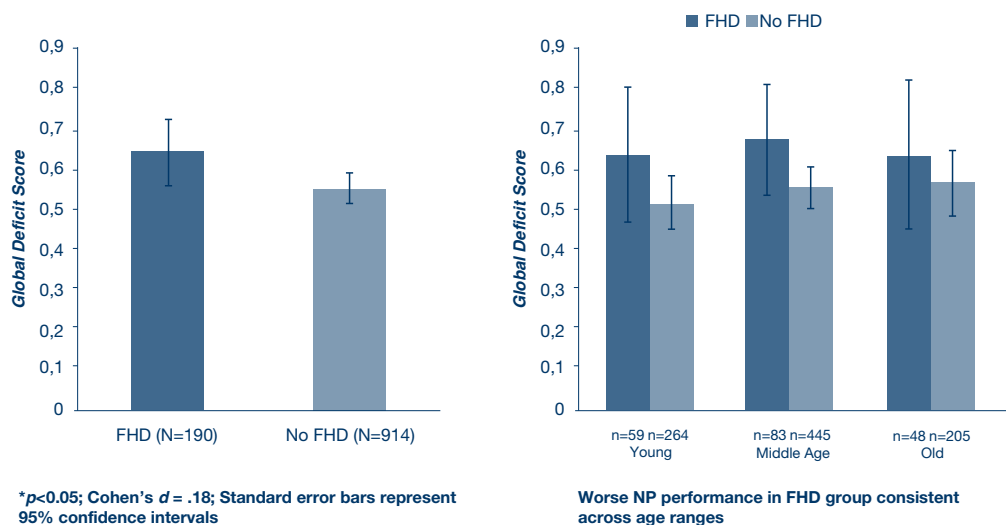
Figure 2. HIV-infected people with a family history of dementia (FHD) had a worse global deficit score on a battery of neuropsychological (NP) tests than did people with no family history of dementia. The difference in global deficit score did not vary greatly by age. (Source: David J. Moore, University of California San Diego.[34])

of dementia (49% versus 36%, P < 0.05). These 190 people also had a higher mean CD4 count than the 914 without a family history (498 versus 433 cells/mm3, P < 0.05) and higher WRAT-III verbal IQ (93.4 versus 90.3, P < 0.05). The two groups did not differ substantially in age (mean 43.6 years with a family history and 43.3 years without a family history), years of education (12.9 and 12.5), percentage of men (73% and 78%), proportion with any lifetime substance abuse or depression (69% and 74%), nadir CD4 count (216 and 200 cells/mm3), or viral load in plasma (2.2 and 2.4 log10 copies/mL) or cerebrospinal fluid (CSF) (1.7 log10 copies/mL in both groups).

The global deficit score was significantly worse in people with a family history of dementia (Figure 2). This pattern was consistent in young, middle-aged, and old individuals but did not grow more marked with age. Among people with a family history of dementia, 53% had HAND, compared with 47% in the group with no family history of dementia. However, proportions of people with HIV-associated dementia, mild neurocognitive disorder, or asymptomatic neuropsychological impairment did not differ significantly by family history of dementia.

For the individual neuropsychological domains assessed, CHARTER members with a family history of dementia had a significantly worse domain deficit score for executive functioning, verbal fluency, and motor skills (P < 0.05). Individuals with a family history of dementia had worse scores—but not significantly worse scores—for the other domains assessed.

Moore and colleagues proposed that a family history of dementia may be a risk factor for development of HAND, despite differences between the groups that are typically protective against neurocognitive deficits (for example, higher estimated verbal IQ). Because the impact of family history of dementia did not differ by age, the CHARTER team suggested that a possible genetic susceptibility to HAND may become manifest at any age. The investigators called for further study to assess the potential relation of a family history of dementia with genetic markers of dementia risk and to determine whether a family history accelerates neuropsychological impairment.

Neurodegenerative marker linked to older age, HIV, and antiretrovirals

Levels of phosphorylated Tau (pTau), a marker of neurodegenerative disease, were higher in CSF of people with HIV than in HIV-negative people, in older people, and in those taking antiretrovirals, according to results of 93-person comparative study.[37]

Tau is a microtubule-associated protein that helps maintain neuronal integrity. Hyperphosphorylation of tau at threonine 181 (pTau) is associated with neurodegenerative disease. But findings on Tau, amyloid, and HAND in people with HIV have been inconsistent. Scott Letendre and University of California, San Diego colleagues planned this study to determine whether HIV infection and older age are associated with higher pTau levels in CSF.

The study involved 70 adults with HIV and 23 without HIV who completed comprehensive neurologic testing, including the Memory for Intentions Test (MIST). Study participants also gave CSF samples to measure pTau and HIV RNA. The investigators calculated CD4 cell recovery as the difference between reported nadir CD4 count and the current count.

Of the 70 people with HIV infection, 53 were taking antiretrovirals and 17 were not. Median age was 36 years in the HIV-negative group and 45 in the HIV-positive group (P = 0.004). A higher proportion of people without HIV (52%) were women, compared with HIV-positive people taking antiretrovirals (11%) or not taking antiretrovirals (18%) (P < 0.001). Median years of education were higher in the HIV-negative group (15) than in the antiretroviral-treated group (13) or the untreated HIV group (12) (P = 0.06). HIV duration was longer in treated than untreated people with HIV (15.8 versus 10.2 years, P = 0.03), and viral load in CSF was lower in the treated group (1.7 versus 3.9 log10 copies/mL, P < 0.001). CD4 nadir was lower in the treated group (146 versus 352 cells/mm3, P = 0.01), and a higher proportion of treated people had an AIDS diagnosis (58% versus 19%, P = 0.005).

Overall median pTau in CSF stood at 45.4 pg/mL (interquartile range [IQR] 32.4 to 60.0) and was significantly higher in people with than without HIV (P = 0.003). Older age correlated positively with higher pTau concentrations (r = 0.25, P = 0.03), most markedly in HIV-infected people taking antiretrovirals. For every year of life, pTau was 0.5 pg/mL higher in people without HIV and 0.8 pg/mL higher in people with HIV. Among people with HIV infection, higher pTau levels were associated with:

- Greater CD4-cell recovery from nadir CD4 count
- Detectable HIV RNA in plasma (t = 2.6, P = 0.01)
- Detectable HIV RNA in CSF (t = 1.9, P = 0.06)
- Caucasian race (t = 1.9, P = 0.07)

Higher pTau concentrations were also associated with worse prospective memory (remembering planned activities) on the MIST summary score (r = -0.25, P = 0.03). Higher pTau was not associated

with worse global neurocognitive performance in this study group. Earlier analyses of Tau and amyloid that focused on global performance may have overlooked associations with memory, the investigators suggested.

In multivariate analysis, higher pTau in CSF was associated with older age (P = 0.03), antiretroviral use (P = 0.06), and antiretroviral use plus CD4-cell recovery (P = 0.05) but not with CD4-cell recovery alone, HIV RNA in plasma or CSF, or race/ethnicity.

Letendre and colleagues concluded that "older people who have HIV disease, use antiretrovirals, and have greater immune recovery have higher pTau levels in CSF, which are associated with worse prospective memory." They proposed that "understanding how age, antiretroviral use, and immune recovery damage neuronal microtubules will be important for developing strategies to protect prospective memory, which is strongly associated with worse everyday functioning outcomes."

Aging markers in brain predict encephalitis in macaques

Two microRNA markers predicted severe encephalitis in SIV-infected macaques.[38] Both markers are associated with aging and are expressed in the brain.

Kenneth Witwer and Johns Hopkins University colleagues noted that the relative contributions of HIV and normal or aberrant aging on HAND prevalence are incompletely understood. As a result, predicting which HIV-positive people run the greatest risk for HAND—and thus merit prophylaxis or closer monitoring—remains difficult. To address this question, the Hopkins researchers sought microRNA markers in plasma that predict encephalitis risk in Macaca nemestrina.

miRNAs, which target regulatory pathways, have attracted attention as potential biomarkers because they are stable in circulation and have proved useful in cancer staging and in therapeutic decisions concerning cancer and HCV infection. For this study, Witwer and colleagues used qRT-PCR cards to profile microRNAs before SIV infection and during acute infection. There were six study animals, three with severe encephalitis after SIV infection and three with no encephalitis.

In samples collected during acute infection, two microRNAs—34a and 125b—had significantly greater expression (P < 0.05) in animals with severe encephalitis than in those with no encephalitis. Both

markers are associated with aging- or senescence-related processes. MicroRNA 125b regulates p53 (a tumor suppressor gene) and is enriched in brain and neurons. Levels of 125b decline in central nervous system tissue throughout SIV infection, while increasing in plasma. MicroRNA 34, which has also been detected in neurons, is regulated by p53 and suppresses the enzyme SIRT1, thus acting in opposition to resveratrol, the SIRT1-stimulating red wine component associated with beneficial cardiovascular effects in mouse and rat models.

Witwer and colleagues suggested that "microRNAs 34a and 125b, alone or in combination with additional biomarkers we have identified, may contribute to development of accurate and easily obtained predictions of HIV/aging-associated neurological disorders." The investigators plan further studies in macaques to see if these and other markers can predict encephalitis risk before infection or with acute samples alone (that is, without preinfection samples). They also hope to validate their findings in humans. If these findings hold true in humans, predicting neurologic disease would be facilitated because microRNAs can be sampled in the peripheral circulation instead of CSF.

HIV/gp120 and aging interact in CNS gene expression in transgenic mice

Genome-wide analysis of central nervous system (CNS) gene expression in transgenic mice expressing HIV/gp120 in brain revealed alterations depending on both genotype and age in this model.[39] Marcus Kaul (Sanford-Burnham Medical Research Institute, La Jolla) and collaborators identified 331 genes affected by HIV/gp120 genotype, age, and the interaction between genotype and age (Figure 3).

Kaul noted that HIV gp120-transgenic mice express viral gp120 in brain and develop neuropathology similar to that seen in humans with AIDS, including loss of neuronal dendrites, loss of synapses, activated microglia, astrocytosis, compromised neurogenesis, and behavioral impairment. The current study compared gp120-expressing mice with mice not expressing gp120 at ages 1.5 months, 3 to 4 months, and 6, 12, and 20 months of age.

In this study, Kaul and coworkers used microarray analysis of whole brain tissue RNA from HIV/gp120 transgene (HIV/gp120tg) and littermate control wild-type mice, with five to six mice in each age group. Of the 21,500 genes analyzed, two-way ANOVA comparison (with a corrected P value cutoff of 0.05) indicated that expression of 3379 genes was significantly affected by genotype (HIV/gp120tg versus control), of 17,280
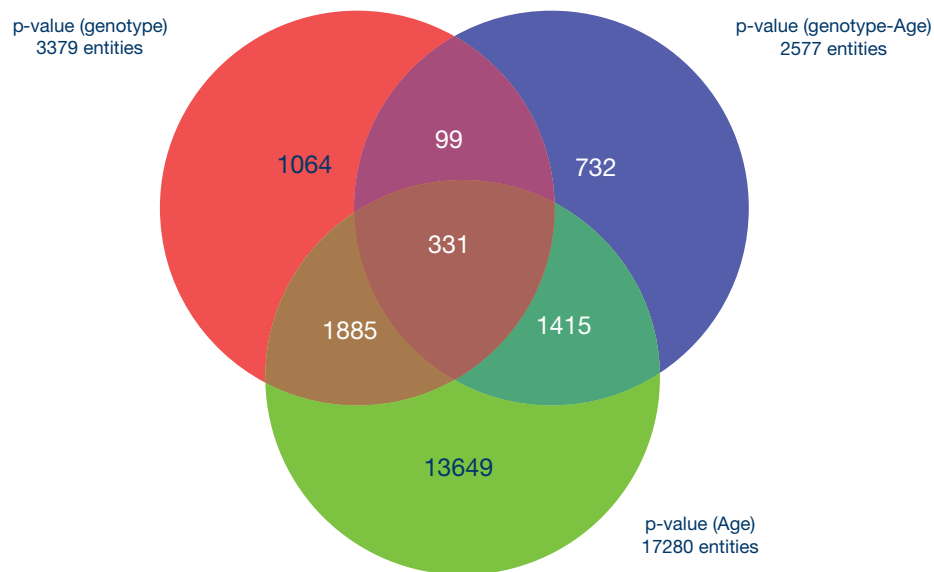
Figure 3. Comparison of HIVgp120tg and littermate control wild-type mice identified 17,280 genes significantly affected by age, 3379 genes affected by genotype, 2577 genes affected by the interaction of age and genotype, and 331 genes affected by all three parameters. (Source: Dr. Marcus Kaul, Sanford-Burnham Medical Research Institute, La Jolla [39])

genes by age, and of 2577 genes by an interaction of genotype and age (Figure 3). There were 331 genes affected by all three parameters.

Among significantly affected genes in 3- to 4-month-old mice, 71 involved neurologic disease, cell death, or organismal injuries and abnormalities. Among significantly affected genes in 20-month-old mice, 67 involved neurologic disease, nervous system development and function, or cell-to-cell signaling and interaction. Pairwise comparison and two-way ANOVA determined that brain expression of genes related to neurologic disease was significantly more frequent in HIV/gp120tg mice than in control mice at 3 to 4 months, 6 months, 12 months, and 20 months of age.

Genes related to nervous system development and function were expressed significantly more often in HIV/gp120tg mice at every age point analyzed. Genes related to nervous system development and function were also differentially expressed in HIV/gp120tg mice at every age analyzed. At various ages, genes involved in metabolic, endocrine, renal, urologic, inflammatory, skeletal, and muscular disorders, as well as hypersensitivity responses, were expressed significantly more frequently in HIV/gp120tg mice.

Kaul and colleagues proposed that their gene expression analysis "indicates that brain injury induced by HIV/gp120 involves not only immune, inflammatory, degenerative and cell death mechanisms but also metabolic, endocrine and developmental pathways." They concluded that "HIV/gp120 and aging interact in

their influence on gene expression and therefore the virus might contribute to aging-dependent cognitive deterioration."

Bone Disease and Vitamin D in HIV infection

Vitamin D plays an essential role in bone formation and, as noted in an invited lecture by Judith Currier (University of California, Los Angeles), a "recent explosion in research" addresses the potential roles of this essential vitamin in immune function, cardiovascular disease, hypertension, malignancy, diabetes, and all-cause mortality.[40] Low and deficient levels of vitamin D have been documented in numerous studies of people with HIV infection, and vitamin D levels correlate inversely with HIV duration.[41] The impact of antiretroviral therapy (especially with efavirenz and PIs) on vitamin D levels remains a topic of intense study.

Currier proposed two vitamin D research priorities in HIV populations: (1) define the efficacy of vitamin D replacement strategies in people beginning or already taking antiretrovirals, especially efavirenz, and (2) examine the relationship between deficiency, replacement, and extraskeletal outcomes. The ongoing Vitamin D and Omega-3 Trial (VITAL) is recruiting 20,000 US men and women to determine whether daily dietary vitamin D supplements (about 2000 IU) or fish oil (about 1 gram of omega-3 fatty acids) lowers the risk of cancer, heart disease, or

stroke in people with no history of these illnesses (www.vitalstudy.org).

In another invited lecture, Todd Brown (Johns Hopkins University) noted that bone formation and resorption occur throughout life, but HIV infection appears to uncouple these tandem processes.[42] Why bone loss increases after antiretroviral therapy begins remains a conundrum, Brown said, because lean mass increases and inflammation decreases after treatment starts. Yet he cited seven longitudinal studies indicating that bone mineral density remains largely stable over a 1- to 2.5-year course of treatment. The list of patient-related risk factors for osteoporosis reads like a catalog of prevalent lifestyle and clinical traits in HIV populations: smoking, alcohol use, opiate use, physical inactivity, low body weight, HCV coinfection, hypogonadism, and low vitamin D. Brown proposed that fractures are "likely to be a major source of morbidity for aging HIV-infected patients."

Age raises fracture risk more in people with than without HIV

Age raised the risk of fracture in people with HIV infection significantly more than in gender-matched HIV-negative controls, according to results of a cohort review involving more than 200,000 people.[43] An earlier comparison of 8525 people with HIV and 2,208,792 people without HIV in a Boston healthcare system found significantly higher fracture prevalence in both men and women with HIV than in uninfected men and women.[44] The new study is the first to assess the impact of age on fracture risk in people with or without HIV infection.

Linda Mundy (GlaxoSmithKline/ViiV Healthcare) used an administrative claims database to compare fracture rates and risks in 59,584 adults with HIV matched 1-to-3 to 178,752 people without HIV. People with HIV were matched to controls by gender, month of enrollment in the claims database, and length of enrollment. All cohort members were in care for at least 12 months from January 1997 through March 2008. The investigators considered only low-impact, nontraumatic fracture codes to calculate incidence per 100 person-years.

Through 13,375 person-years of follow-up, 9027 people (3.8%) had a fracture. Fracture incidence was 14% higher in the HIV-positive group than in the HIV-negative group (incidence rate ratio of 1.14, 95% CI 1.09 to 1.20). Compared with HIV-negative controls, the HIV group had a doubled risk of fracture (hazard ratio [HR] 2.02, 95% CI 1.94 to 2.1).

Five variables independently affected fracture incidence for the whole study group in a multivariate model:

- Prior fracture:
  HR 4.49, 95% CI 3.89 to 5.18
- Excess alcohol:
  HR 1.90, 95% CI 1.65 to 2.20
- Low physical activity:
  HR 1.77, 95% CI 1.73 to 1.82
- Anti-osteoporosis bisphosphonate use:
  HR 1.49, 95% CI 1.29 to 1.72
- Low weight:
  HR 1.32, 95% CI 1.18 to 1.48

Linear trend analysis of fracture risk that considered three age groups (under 30, 30 to 59, and over 59) found an increased fracture risk with advancing age in people with HIV but without AIDS (P = 0.012) and in people with AIDS (P = 0.001), compared with HIV-negative people.

In a model that stratified people into the three age groups, two factors independently predicted fracture in the youngest group—prior fracture (HR 7.77, 95% CI 3.23 to 18.67) and excess alcohol (HR 2.24, 95% CI 1.06 to 4.74). In 30-to-59-year-old people, eight variables independently predicted fracture:

- HIV infection without AIDS:
  HR 1.18, 95% CI 1.09 to 1.28
- HIV with AIDS:
  HR 1.15, 95% CI 1.06 to 1.26
- Prior fracture:
  HR 3.81, 95% CI 3.14 to 4.63
- Low activity:
  HR 2.24, 95% CI 1.90 to 2.65
- Excess alcohol:
  HR 1.86, 95% CI 1.55 to 2.23
- Antiosteoporosis bisphosphonate exposure:
  HR 1.36, 95% CI 1.20 to 1.68
- Low weight:
  HR 1.30, 95% CI 1.12 to 1.50
- Vitamin D deficiency and supplementation of vitamin D or calcium:
  HR 0.72, 95% CI 0.54 to 0.98

The study did not clarify why the last factor was protective. Among people older than 59, prior fracture (HR 2.79, 95% CI 1.68 to 4.64) and low activity (HR 2.65, 95% CI 1.67-4.21) independently predicted fracture.

Considering potential biases inherent in any retrospective study, Mundy and colleagues concluded that fracture risk increases with advancing age in HIV-positive people with or without AIDS, compared with an HIV-negative control group, and that this finding has "potential implications for clinical practice and preventive medicine."

HIV-associated lipoatrophy may play role in vitamin D deficiency

HIV-related lipoatrophy or current efavirenz was associated with vitamin D deficiency in a cohort review in Windsor, Ontario.[45] The study is the first to define a link between low vitamin D and lipoatrophy, which could affect vitamin D synthesis in skin upon exposure to the sun.

Windsor is the southernmost city in Canada, near Detroit, Michigan. The study presented by Linda Robinson (Windsor Regional Hospital) was a chart review of the entire HIV Care Program database in Windsor, which includes data on age, race, CD4-cell nadir, current CD4 count and viral load, body mass index, lipoatrophy, current smoking status, 25OH vitamin D, and antiretroviral therapy. Robinson and colleagues hypothesized that, since sunlight-associated vitamin D is synthesized in skin and atrophic skin changes may cause vitamin D deficiency in older populations, HIV-associated lipoatrophy may affect vitamin D levels and contribute to vitamin D deficiency in people with HIV.

For statistical analysis, the investigators examined log-transformed vitamin D levels as a continuous measure in a multiple linear regression analysis. They defined vitamin D deficiency as a level below 50 nmol/L (20 ng/mL) and adequate vitamin D as 75 nmol/L (30 ng/mL) or higher. Among 217 patients with complete data, age averaged 45.5 years (+/- 11.2 standard deviation), 76% were white, 78% were men, half were current smokers, and body mass index averaged 26.4 kg/m2 (+/- 4.7). Sixty-nine people, about one third of those with complete data, had self-reported or physician- or nurse-reported lipoatrophy.

Median nadir CD4 count stood at 163 cells/mm3 (range 1 to 568), 172 people (79%) had a viral load below 50, 136 (63%) had taken zidovudine or stavudine, 90 (42%) were currently taking efavirenz, and 71 (33%) were currently taking a protease inhibitor. Vitamin D (25OHD) levels for the group averaged 69

nmol/L, 33% had a level below 50 nmol/L, and 65% had a level below 75 nmol/L.

Six variables were associated with lower vitamin D in a multiple linear regression model: lipoatrophy (β coefficient -0.063, P = 0.035), age below 50 years (β coefficient -0.056, P = 0.037), nonwhite race (β coefficient -0.182, P < 0.001), vitamin D measured from November through April (β coefficient -0.086, P = 0.001), current efavirenz (β coefficient -0.061, P = 0.005), and any use of zidovudine or stavudine, the nucleosides most strongly associated with lipoatrophy (β coefficient -0.059, P = 0.041). Four variables independently raised the risk of vitamin D deficiency, including lipoatrophy (Table 2).

Robinson noted that the study is limited by its size and cross-sectional design, by subjective clinical assessment of lipoatrophy, and by vitamin D assessment throughout the year (though most samples were drawn between July and November). The investigators believe their findings "suggest that skin synthesis of vitamin D may be affected by previous antiretroviral exposure" and that the results identify a group of HIV-positive patients who require screening.

Earlier research on whether efavirenz affects vitamin D levels yielded divergent results. A 1077-person cross-sectional study in London, United Kingdom, found an association between current efavirenz and severe vitamin D deficiency (below 25 nmol/L),[46] while a 51-person US study linked starting a first-line efavirenz regimen with significant declines in vitamin D.[41] In contrast, a 312-person cross-sectional study at another London (UK) HIV clinic found no correlation between any antiretrovirals and low vitamin D concentrations.[47]

Whether measuring vitamin D levels in people with HIV has clinical utility remains controversial. Todd Brown of Johns Hopkins University, who studies bone mineral density in people with HIV, noted at

Table 2. Independent predictors of vitamin D deficiency (<50 nmol/L) in an Ontario HIV cohort

Variable	Odds ratio	95% CI	P
Lipoatrophy	3.75	1.7 to 7.2	0.001
Nonwhite race	7.5	3.4 to 16.5	<0.001
November-April vitamin D measurement	2.9	1.5 to 5.7	0.002
Current efavirenz	2.0	1.0 to 3.8	0.044

Source: Dr. Linda Robinson, Windsor Regional Hospital, Canada.[45]

the workshop that if you look for vitamin D deficiency in HIV-positive people, you will find it; and if you supplement deficient patients, you will raise vitamin D levels; but "whether you're doing anyone a favor is still an open question."

HIV, Age and other Outcomes

Reasons for hospital admission differ by age in HIV group

Compared with HIV-positive people under 50 years old, those 50 or older got admitted to the hospital more for cardiovascular and gastrointestinal diseases, and for all causes combined, according to results of a cohort study in four US cities.[48] Throughout the 2001-2008 study, admissions for AIDS-defining illnesses dropped, while admissions for cardiovascular disease and non-AIDS infections rose.

Stephen Berry (Johns Hopkins University) and HIV Research Network colleagues planned this study to assess hospital admission rates stratified by diagnostic category in HIV-positive people younger than 50 or 50 and older. Cohort members were seen in clinical practice from 2001 through 2008 in Baltimore, New York City, Portland, and San Diego. The investigators ascertained reasons for admission by admission data and ICD-9 codes.

The analysis included 11,546 HIV-positive patients in care for a median of 3 years. In the 50-and-older group, the number of people in care rose from 713 in 2001 to 1695 in 2008, while the younger group had 4143 people in care in 2001 and 3489 in 2008. Median age in the older group stood at 51 years in both 2001 and 2008, while median age in the younger group rose from 39 to 42 over the study period. In 2001 and 2008, proportions of women in the older group were 22% and 27%, and in the younger group 29% and 27%. About 40% in both groups were black, 40% white, and 20% Hispanic. In 2008 HIV transmission risks were evenly distributed in the older group (32% men who have sex with men [MSM], 30% injection drug use, and 26% heterosexual), while in the younger group MSM predominated in 2008: 42% versus 16% injection drug use and 27% heterosexual. Current CD4 count and proportion with a viral load below 400 copies/mL rose steadily in older and younger cohort members across the study period.

In univariate analysis, the all-cause hospitalization rate fell in both groups from 2001 through 2008. In multivariate analysis, calendar time was no longer associated with all-cause hospitalization rate, but several other factors were significantly associated: age 50 or over (incidence rate ratio [IRR] 1.37, 95% CI 1.27 to 1.49), female gender (IRR 1.23, 95% CI 1.13 to 1.33), being black (IRR 1.40, 95% CI 1.29 to 1.52) or Hispanic (IRR 1.16, 95% CI 1.04 to 1.29) rather than white, and acquiring HIV through injection drug use rather than sex between men (IRR 1.66, 95% CI 1.54 to 1.79). Lower CD4 count and higher viral load were also associated with a higher hospital admission rate.

Among people 50 and older, the most frequent causes of hospital admission were non-AIDS infections (between 8 and 9 per 100 person-years) and cardiovascular disease (5 per 100 person-years),
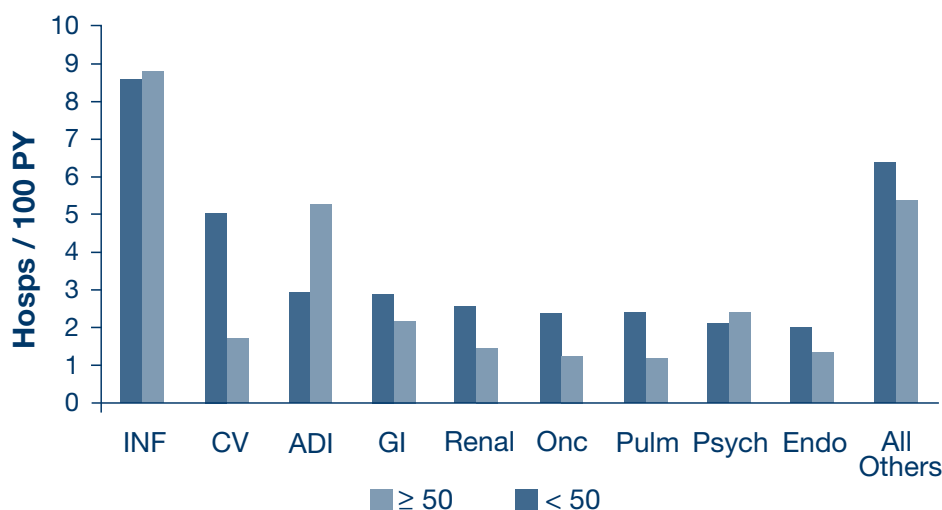
INF, non-AIDS defining infections; **CV,** cardiovascular; **ADI,** AIDS defining illnesses
All Others: injury/poison, symptom, heme, neuro, ortho, missing, derm, congenital

Figure 4. Reasons for hospital admission in HIV-positive people in four US cities differed by age from 2001 through 2008. (Source: Dr. Stephen Berry, Johns Hopkins University, Baltimore.[48])

followed by AIDS-defining illness, gastrointestinal/ liver disease, renal disease, cancer, pulmonary disease, psychiatric diagnoses, and endocrinologic/ metabolic disease (all between 2 and 3 per 100 person-years). Hospital admission rates for non-AIDS infections were equivalent in the older and younger groups, while older people were admitted more often for cardiovascular or gastrointestinal/liver disease and younger people were admitted more often for AIDS-defining conditions (Figure 4).

Multivariate analysis determined that several factors were independently associated with hospital admissions for non-AIDS infections—lower CD4 count, higher viral load, injection drug use, black race, and female gender. After statistical adjustment for the rise in CD4 count and the increase in patients with an undetectable viral load over time, the rate of non-AIDS infections increased over the years. Being 50 or older did not raise the risk of hospital admission for non-AIDS infections. Among people 50 and older, the most frequent non-AIDS infectious diagnoses were bacterial pneumonia (7.5% of all admissions), cellulitis (3.3%), and sepsis (1.7%). Respective percents in the younger group were 7.0%, 4.1%, and 2.2%.

Being 50 or older nearly tripled the risk of hospital admission for cardiovascular disease compared with younger people (IRR 2.74, 95% CI 2.24 to 3.34). CD4 count, viral load, black race, female gender, injection drug use, and later calendar time also made admission for cardiovascular disease more likely. The most frequent cardiovascular diagnoses were heart failure (2.7% and 1.1% of all admissions in the older and younger groups,), coronary events (2.5% and 0.5%), and chest pain (2.2% and 0.8%).

People 50 and older had a significantly higher risk of hospital admission for gastrointestinal/liver complications than younger people (IRR 1.43, 95% CI 1.18 to 1.73). Lower CD4 count, injection drug use, and Hispanic ethnicity also made a gastrointestal disease admission more likely. The most frequent gastointestinal diagnoses were pancreatitis (1.4% of all admissions in both age groups), gastrointestinal bleeding (1.2% and 0.6% in the older and younger groups), and cirrhosis (0.9% and 0.6% in the older and younger groups).

Berry and colleagues concluded that HIV-positive people 50 and older are hospitalized most often for non-AIDS infections, cardiovascular disease, AIDS-defining illnesses, and gastrointestinal disease, and that all-cause, cardiovascular, and gastrointestinal admissions are significantly more frequent in people 50 or older than in younger patients. Because of the high non-AIDS infection rates, especially in older people,

the investigators urged clinicians to recommend pneumonia and flu vaccinations for people with HIV. They noted that the high cardiovascular admission rates validate ongoing research on cardiovascular risk in people with HIV infection. They suggested that future research examine novel ways to prevent non-AIDS infections in older people living with HIV.

Women with HIV notice aging symptoms more often than men
Four out of five women seen at a Barcelona HIV clinic thought they were suffering from premature aging, while fewer than 20% of men in the clinic had that impression.[49] Higher proportions of women than men complained of most aging-related symptoms assessed, including mood disorders and mobility-related complaints.

Carmina R. Fumaz, Eugènia Negredo, and coworkers at Germans Trias i Pujol University Hospital noted that proportions of middle-aged and older people with HIV are increasing, but aging-related symptoms and their impact on daily life often are not assessed in routine care of these patients. Therefore they planned this cross-sectional study of 60 men and 40 women infected with HIV for at least 15 years. The researchers developed a study-specific questionnaire that included 19 symptoms rated on a 5-point scale for intensity and limitation on daily living. Study participants were also asked whether they believed they were aging prematurely.
Age of study participants averaged 48.2 +/- 7.3 years and did not differ between men and women. The group had been infected with HIV for an average of 18.5 years and had an average nadir CD4 count of 198.3 cells/mm3 and an average current CD4 count of 573.4 cells/mm3. Seventy-eight study participants had a viral load below 25 copies/mL, and 42 had HCV infection. Rates of these variables did not differ significantly between women and men.
High proportions of both women and men complained of aging-related symptoms, but significantly higher proportions of women complained of numerous symptoms:
- Fatigue:
  100% of women vs 85% of men, P = 0.04
- Anxiety:
  92% of women vs 76% of men, P = 0.04
- Sadness:
  91% of women vs 72% of men, P = 0.02
- Difficulty sleeping:
  91% of women vs 74% of men, P = 0.04
- Mobility difficulty:
  82% of women vs 61% of men, P = 0.02
- Hair thinning:
  74% of women cs 48% of men, P = 0.01

Symptom intensity scores for mobility difficulty, joint pain, balance, dry skin, hair thinning, sadness, anxiety, and loss of sexual interest were all significantly higher among women than men (Figure 5). Overall 57 study participants (57%) believed they were aging prematurely, but the proportion was significantly higher among women than men (80% versus 18%, P < 0.001). Seventy study participants felt symptoms were limiting their personal life, including 82% of women and 63% of men (P < 0.04). A significantly higher proportion of women than men also thought symptoms were limiting their work activity (77% versus 53%, P < 0.04).
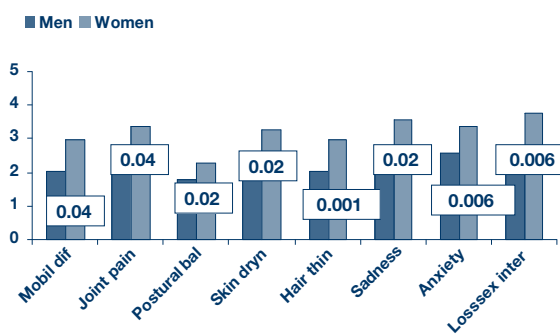

Figure 5. Compared with men seen at a Barcelona HIV clinic, women gave higher intensity scores to an array of aging-related symptoms on a 1-to-5 scale. (Source: Dr. Eugenia Negredo, Germans Trias i Pujol University Hospital, Spain[49])

The researchers concluded that aging-related symptoms affect high proportions of women and men infected with HIV for 15 years or more, despite good viral control and CD4 counts. Higher proportions of women than men complained of many symptoms, women gave several symptoms a higher intensity score, and a higher proportion of women believed they were aging prematurely.

Negredo noted that women in many cultures may be more apt than men to voice clinical and psychological complaints. Yet symptom prevalence and intensity were high in both men and women in this study, and high proportions believed these symptoms interfered with daily living. The researchers proposed that their results suggest women "could be more vulnerable to the impact of these clinical manifestations" than men.

Older men with HIV report sexual dysfunction more than men with diabetes

HIV-positive men 50 or older complained of sexual dysfunction significantly more often than older HIV-negative men with chronic diabetes mellitus or men with no severe chronic disease, according to results of a German cross-sectional study.[50] Compared with the control group, men with HIV and men with diabetes had higher scores reflecting severity of aging-related complaints.

The German 50/2010 cohort study involves patients from 37 HIV outpatient clinics and private practices across Germany. This analysis focused on 175 men with HIV, 165 HIV-negative men with type 2 diabetes, and 165 men without a severe chronic disease. Everyone in the HIV group had been infected longer than 1 year. Patients with HIV, patients with diabetes, and control group members could have hypertension, hyperlipidemia, HBV or HCV virus infection, depression, a history of myocardial infarction, and certain other conditions. No study participants had acute life-threatening disease or malignant disease.

All study participants completed the Aging Male Symptom Scale (AMS), a self-reported questionnaire with 17 items addressing psychological, physical, and sexual symptoms. Items are scored 1 to 5, and a score of 37 or higher indicates moderate or severe subjectively perceived complaints. Study participants also completed the AMS sexual subscale (AMS-S), a five-item questionnaire in which a total score of 11 or higher indicates severe reduction of sexual function.

Median age was higher in the diabetes group (59.1) than in men with HIV (57.7) or the control group (57.1) (P = 0.006). Median body mass index was higher in men with diabetes (30 kg/m2) than in control men (26 kg/m2) or men with HIV (24 kg/m2) (P < 0.001). Nearly two thirds (65%) of men with diabetes had a body mass index above 28 kg/m2, while only 27% of controls and 17% of men with HIV had a body mass index that high (P < 0.001). Stable partnerships were more common in the control group (73%) and the diabetes group (68%) than in the HIV group (49%) (P < 0.001).

Median total AMS score was 37 in men with HIV, higher than median scores of 34 in men with diabetes and 31 in control men (P < 0.001). While half of men with HIV had moderate or severe perceived AMS symptoms (a score of 37 or higher), 45% of men with diabetes and 28% of controls had a score that high (P < 0.001). A multivariate model that considered HIV infection, diabetes, body mass index, stable partnership, and age groups (60 to 69 and 70 to 79 versus 50 to 59) determined that three factors independently raised

the risk of a total AMS score of 37 or higher:

- HIV infection vs no HIV:
  odds ratio (OR) 2.2, 95% CI 1.4 to 3.4, P < 0.001
- Diabetes vs no diabetes:
  OR 1.9, 95% CI 1.2 to 3.0, P < 0.01
- Without stable partnership:
  OR 1.7, 95% CI 1.2 to 2.6, P < 0.01

Median AMS-S scores were 11 in the HIV group, 10 in the diabetes group, and 9 in the control group (P < 0.001). While 52% of men with HIV had an AMS-S score of 11 or higher (indicating severe reduction in sexual function), 48% of men with diabetes and 33% of control men had an AMS-S score that high (P < 0.001). Multivariate analysis identified two factors that independently predicted an AMS-S score of 11 or higher:

- HIV infection versus no HIV:
  OR 2.1, 95% CI 1.4 to 3.3, P = 0.001
- Age 70 to 79 versus 50 to 59:
  OR 4.5, 95% CI 2.4 to 8.3, P < 0.001

Mike Youle, an HIV researcher and clinician at London's Royal Free Centre for *HIV* Medicine, noted that because the three study groups were not matched on sexual preference, the HIV group probably included a much higher proportion of MSM than the other groups. In his experience, Youle noted that gay men perceive sexual dysfunction differently from heterosexual men, and that perception may affect AMS-S scores in this study.

Low malignancy risk with maraviroc sustained in older age groups

Malignancy incidence was lower in antiretroviral-naive and experienced patients older than 50 who took the CCR5 antagonist maraviroc in four trials than in people who took comparator regimens.[51] Multivariate analysis determined that older age raised the risk of a new cancer diagnosis in these trial participants, so they did not differ from other populations in that way.

During clinical trials of vicriviroc, a CCR5 antagonist no longer in development, concern arose that malignancies might occur more often in people taking vicriviroc than in those taking regimens excluding this agent.[52] Although malignancy rates were not unusually high among people taking maraviroc in clinical trials, a generally higher cancer incidence can be expected in the aging HIV population. Therefore Simon Portsmouth and ViiV Healthcare colleagues planned this study to determine cancer incidence according to age in trial participants taking maraviroc or other regimens in four randomized studies.

The four trials analyzed were MOTIVATE 1 and 2 (maraviroc versus placebo plus optimized background regimen in antiretroviral-experienced patients with CCR5-using virus), MERIT (maraviroc versus efavirenz plus zidovudine/lamivudine in antiretroviral-naive patients with CCR5-using virus), and study A4001029 (maraviroc versus placebo plus an optimized background regimen in antiretroviral-experienced patients with non-CCR5-using virus). The new analysis included both blinded and open-label phases of all trials (except for the placebo group in the open-label phase of the MOTIVATE studies). Portsmouth and colleagues classified tumors as AIDS-defining or non-AIDS-defining and as infection-related or non-infection-related. The investigators divided study participants into three age groups: under 30, 30 to 50, and over 50.

Overall the analysis involved 1499 people taking maraviroc (294 of them over 50 years old) and 631 taking a comparator regimen (100 of them over 50). Exposure-adjusted malignancy incidence was lower in the combined maraviroc arms than in comparator arms across all four studies.

In the MOTIVATE trials, exposure-adjusted incidence rate ratios were significantly lower in maraviroc arms for the overall analysis, for AIDS-defining malignancies, and for infection-related malignancies; rate ratios were never significantly higher in the placebo groups:

- Overall:
  IRR 0.46, 95% CI 0.22 to 0.95
- AIDS-defining malignancies:
  IRR 0.18, 95% CI 0.06 to 0.54
- Non-AIDS-defining malignancies:
  IRR 0.84, 95% CI 0.30 to 2.40
- Infection-related malignancies:
  IRR 0.28, 95% CI 0.12 to 0.63
- Non-infection-related malignancies:
  IRR 2.36, 95% CI 0.32 to 17.55

Multivariate analysis of data from all four studies determined that every 25-cell/mm3 on-treatment increase in CD4 count independently lowered the risk of a new malignancy (HR 0.908, 95% CI 0.861 to 0.957), as did reaching a viral load below 50 copies/mL (HR 0.262, 95% CI 0.142 to 0.482). Each additional year of age independently raised the new-malignancy risk (HR 1.085, 95% CI 1.055 to 1.116), as did sexual transmission of HIV between men (HR 1.874, 95% CI 1.014 to 3.465). These risk factors held true regardless of treatment arm. The higher malignancy risk in MSM compared with other HIV transmission groups was driven by anal cancer.
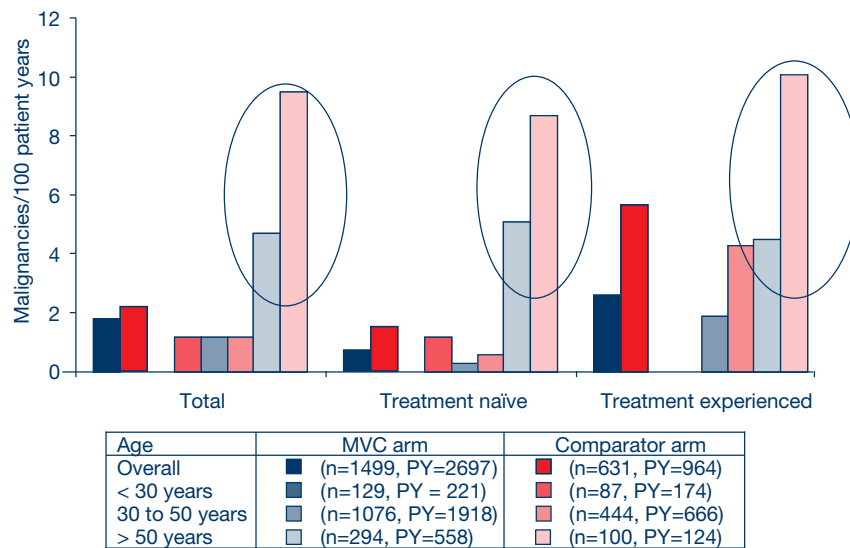
Age	MVC arm	Comparator arm
Overall	■ (n=1499, PY=2697)	■ (n=631, PY=964)
< 30 years	■ (n=129, PY = 221)	■ (n=87, PY=174)
30 to 50 years	■ (n=1076, PY=1918)	■ (n=444, PY=666)
> 50 years	■ (n=294, PY=558)	■ (n=100, PY=124)

MVC, maraviroc; PY, patient years.

Figure 6. In HIV-infected trial participants over 50 years old, antiretroviral exposure-adjusted malignancy incidence was substantially lower in maraviroc recipients in four randomized trials than in comparator arms in those trials. (Source: Dr. Simon Portsmouth, ViiV Healthcare, New York[51])

As expected, new malignancies proved most frequent in people older than 50. However, cancer incidence was numerically lower in maraviroc arms than in comparator arms in people over 50 across all four studies analyzed. Also, the between-arm incidence difference favoring maraviroc was greater in the over-50 group than in 30-to-50-year-olds (Figure 6). The age-related difference also favored maraviroc recipients in analyses of non-AIDS cancers, AIDS cancers, and infection-related cancers.

Portsmouth and colleagues concluded that maraviroc-treated patients have a low incidence of malignancy regardless of antiretroviral experience or HIV coreceptor use. Reduced malignancy incidence in maraviroc recipients compared with comparator arm patients was especially striking in people older than 50.

Age, HIV, Polypharmacy, and Polypathology

High comorbidity burden with HIV and resulting polypharmacy

People with HIV infection had more non-HIV comorbidities than matched controls without HIV in a large Italian case-control comparison, and daily pill burden was higher in the HIV group regardless of age.[53] Yet among people with multiple comorbid conditions, polypharmacy, defined as treatment with five or more drugs daily, was significantly less common in the HIV group.

Giovanni Guaraldi (University of Modena and Reggio Emilia) and colleagues hypothesized that age-related noninfectious comorbidities—including cardiovascular diseases, hypertension, type 2 diabetes mellitus, renal failure, and fractures—require treatment with multiple non-HIV medications. They planned this study to compare polypathology, its treatment, and pill burden in 2854 HIV-positive patients and 8562 controls matched for age, gender, race, and geographical region. Controls came from the CINECA ARNO database, which records vital statistics, prescriptions, hospital admissions and discharges, and diagnostic tests and examinations in 11 million people across Italy. All HIV-positive people had antiretroviral experience, and all cases and controls were seen from 2002 to 2009.

Age averaged 45.9 years (+/- 7.6) for the combined study groups, and 37.1% were women. Defining polypathology as simultaenous occurrence of two or more of the five comorbidities, Guaraldi and coworkers charted a higher prevalence of polypathology in both cases and controls in each higher age group (Table 3). Polypathology prevalence was greater among HIV-positive people in every age stratum.

To classify treatment of cases and controls, the investigators used the Anatomical Therapeutic Chemical (ATC) classification system. Analyzing 13,778 drug records for cases and 12,619 for controls, they found that higher proportions of people with HIV were taking alimentary tract and metabolism drugs, including drugs for liver disease, antidiarrheals, and proton pump inhibitors (26% versus 17%, P < 0.001);

Table 3. Polypathology by age in HIV-positive cases and HIV-negative controls

Age	HIV-positive (n = 2854)	HIV-negative (n = 8562)
40 or younger	3.9%	0.5%
41 to 50	9.0%	1.9%
51 to 60	20.0%	6.6%
Older than 60	46.9%	18.7%

Polypathology defined as two or more comorbid conditions, including cardiovascular diseases, hypertension, type 2 diabetes mellitus, fracture, and renal failure.
Source: Dr. Giovanni Guaraldi, University of Modena, Italy.[53]

nervous system drugs, including psychoanaleptics and antiepileptics (14% versus 11%, P < 0.001); and antineoplastic and immune modulating agents, including interferon (2% versus 1%, P = 0.003). More frequent use of these medications in HIV-positive patients held true across the four age brackets analyzed. People without HIV received treatment more often with cardiovascular drugs (42% versus 40%, P = 0.011), genitourinary agents and sex hormones (5% versus 2%, P < 0.001), and respiratory system drugs (4% versus 0%, P < 0.001).

Hypertension prevalence rose with age in both cases and controls, with no significant difference in prevalence between cases and controls in any age group (Figure 7). Yet in each age stratum, a substantially lower proportion of HIV-positive patients were receiving antihypertensive therapy (Figure 7).

HIV-positive people in all four age strata received sex hormone therapy and medications for urologic conditions significantly less often than HIV-negative controls (P < 0.001 for all comparisons). The HIV group received treatment for obstructive lung airway disease more often than HIV-negative controls if they were 50 or under (P = 0.029) or older than 50 (P = 0.063). But systemic antihistamines were used more often by HIV-negative controls than HIV-positive cases in the 50-and-under age bracket (P = 0.029) and the over-50 bracket (P = 0.063).

Analysis of daily pill burden excluding antiretrovirals found a significantly higher burden in the HIV group in each of the four defined age strata. Analysis including
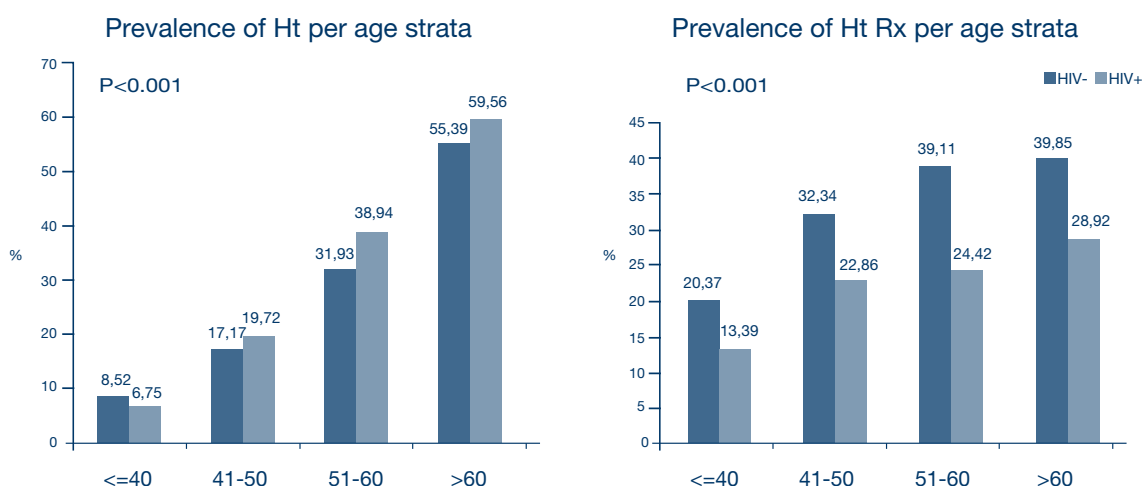

Figure 7. Prevalence of hypertension (Ht) was similar in Italian patients with and without HIV infection in a large case-control comparison. But HIV-positive patients received antihypertensive therapy less often than HIV-negative controls in every age bracket. (Source: Dr. Giovanni Guaraldi, University of Modena, Italy.[53])

antiretrovirals showed an accordingly higher median daily burden in the HIV group and even greater between-group differences:

- Under 40 years:
  4.0 with HIV vs 0.00 without HIV (P < 0.001)
- 41 to 50 years:
  6.0 with HIV vs 0.27 without HIV (P < 0.001)
- 51 to 60 years:
  6.0 with HIV vs 0.88 without HIV (P < 0.001)
- Over 60 years:
  9.0 with HIV vs 0.93 without HIV (P < 0.001)

Logistic regression analysis indicated that people with HIV were significantly more likely to have multiple noninfectious comorbid conditions than matched controls without HIV (P < 0.001). But among patients with multiple comorbidities, polypharmacy (five or more drugs a day) proved significantly less likely in HIV-positive people (P < 0.001).

Guaraldi and colleagues concluded that undertreatment of comorbid conditions is more common in HIV-positive people than in matched controls without HIV. However, pill burden is higher in the HIV group, even when antiretrovirals are excluded from the analysis. The study does not address whether the observed undertreatment of HIV-positive people for comorbid conditions is explained more by underprescribing by HIV physicians or by reluctance of HIV-infected people to add more drugs to their regimen.

Higher drug interaction potential in 60-or-older HIV patients in Ontario

HIV outpatients 60 years old or older took more medications (including antiretrovirals and other drugs) than younger patients seen at the same Toronto tertiary care center clinic.[54] Potential drug-drug interactions were more likely in the 60-and-older group than in younger patients.

Alice Tseng (Toronto General Hospital) reported that 12.2% of AIDS patients in Canada were 50 or older at the end of 2006. From 1985 through 2008, 8.9% of people with newly diagnosed HIV infection were 50 or older and 2.3% were 60 or older. Median age of patients in the Toronto General Hospital Immunodeficiency Clinic rose from 38 in 1996 to 47 in 2009. The proportion of patients 60 and older rose from 2% in 1996 to 10.3% in 2009.

Tseng and colleagues planned this retrospective analysis of clinic patients to compare the median number of prescription and nonprescription drugs used by patients 60 and older versus younger patients and to assess the likelihood of potential drug-drug interactions in the two groups. The investigators classified drugs by the Anatomical Therapeutic Chemical (ATC) system. The analysis included 566 people who tested positive for HIV between 1 January 1996 and 31 December 2009, including 38 people (7%) who were 60 or older.

Median age of the older group was 65 (IQR 62 to 69), compared with 44 (IQR 37 to 49) in the younger group. There quarters of each group were men, and

Table 4. Non-HIV medication use in older and younger age groups in Toronto

	<60 years (n = 528)	>60 years (n = 38)	P
Gastrointestinal medications*	38%	63%	<0.01
Cardiovascular medications	24%	55%	<0.0001
Anticoagulants/antiplatelets	7%	18%	0.01
Erectile dysfunction agents	1%	5%	0.06
Systemic hormonal agents	5%	16%	0.01
Musculoskeletal agents	9%	24%	<0.01
Narcotics/analgesics	17%	39%	<0.001
Anticonvulsants	7%	16%	0.06
Psychotropics	30%	34%	0.54

*Includes antidiabetics.
Source: Dr. Alice Tseng, Toronto General Hospital, Canada.[54]

median current CD4 count was similar in older and younger people (496 and 475 cells/mm3). The older group had a larger proportion with a viral load below 50 copies/mL (89% versus 74%, P = 0.03), a higher proportion of Caucasians (65% versus 47%, P = 0.06), a lower proportion from HIV-endemic countries (19% versus 35%, P = 0.05), a lower proportion of immigrants (13% versus 30%, P = 0.02), an earlier year with a positive HIV test (2001 versus 2003, P < 0.01), and an earlier year of first antiretroviral therapy (2002 versus 2004, P = 0.04).

Median number of prescription or nonprescription drugs taken was significantly higher in the 60-and-older group (7, IQR 5 to 11) than in the younger group (4, IQR 3 to 7) (P < 0.0001). Proportions of people taking drugs from current antiretroviral classes did not differ between age groups. However, older people were significantly more likely to take gastrointestinal medications, cardiovascular medications, anticoagulants/antiplatelets, erectile dysfunction drugs, systemic hormonal agents, musculoskeletal agents, narcotics/analgesics, and anticonvulsants (Table 4).

Four potential drug-drug interactions were significantly more likely in people 60 and older, and there was a trend toward a greater likelihood for one interaction:

- Nonnucleosides or protease inhibitors plus cardio-vascular drugs:
  42% of older patients versus 20% of younger patients, P = 0.003
- Nonnucleosides or protease inhibitors plus anti-convulsants:
  16% of older patients versus 5% of younger patients, P = 0.02
- Protease inhibitors plus cardiovascular drugs:
  34% of older patients versus 13% of younger patients, P = 0.001
- Protease inhibitors plus warfarin:
  8% of older patients versus 1% of younger patients, P = 0.01
- Protease inhibitors plus anticonvulsants:
  11% of older patients versus 4% of younger patients, P = 0.09

The investigators noted that the drug database may not accurately reflect each patient's complete medication history (for example, reported proportions taking erectile dysfunction drugs seem low) and that clinicians may have adjusted doses for some of the potential drug-drug interactions identified. The study did not assess adverse outcomes of drug interactions.

Tseng and colleagues concluded that 60-and-older patients in their clinic were taking more drugs than younger patients, and that the greater drug burden in older people posed a higher risk of potential drug-drug interactions. The researchers urged HIV clinicians to avoid potential drug interactions by consulting with pharmacists or pharmacologists and by referring to reliable drug interaction databases. (Three widely used antiretroviral drug interaction databases are listed in the references.[55-57])

Comorbidity rates higher in HIV group than HIV-negative controls at earlier age

A large case-control comparison of people with and without HIV infection found that HIV-positive people in their 40s had multiple noninfectious comorbidities as often as HIV-negative controls in their 50s.[58] And HIV-positive people in their 50s had multiple comorbidities as often controls in their 60s. Lower CD4 nadir and longer antiretroviral duration predicted multiple comorbidities.

Giovanni Guaraldi (University of Modena and Reggio Emilia) and collaborators planned this study to compare prevalence of common age-related comorbidities in 2854 people with HIV and 8562 controls matched for age, gender, race, and geographic region. The HIV population came from the University of Modena Metabolic Clinic or an HIV outpatient clinic. Metabolic clinic patients did not differ from outpatient clinic patients in rates of the five comorbid conditions analyzed—cardiovascular disease, hypertension, type 2 diabetes mellitus, fracture, and renal failure. Controls came from the CINECA ARNO Observatory database, a nationwide initiative that records vital statistics, prescriptions, hospital admissions and discharges, and diagnostic tests for 11 million people in Italy. All HIV-positive people had antiretroviral experience, and all cases and controls were seen from 2002 to 2009.

Because of age and gender matching, average age (45.8 +/- 7.5) and proportion of women (37.1%) were the same in both groups. The HIV group had been infected for a median of 196 months (IQR 136 to 248), their median nadir CD4 count was 170 cells/mm3 (IQR 66 to 263.5), and their median current CD4 count stood at 544 cells/mm3 (IQR 390 to 724). Nearly three quarters of people with HIV (71.3%) had an undetectable viral load.

Prevalence of each of the five comorbidities was significantly higher in the HIV group (P < 2.2-16 for all comparisons with controls). Defining polypathology as two or more simultaneous comorbidities, the investigators recorded higher polypathology prevalence in the HIV group in every age stratum analyzed (Figure 8). Notably, polypathology prevalence in 41- to 50-year-old people with HIV was
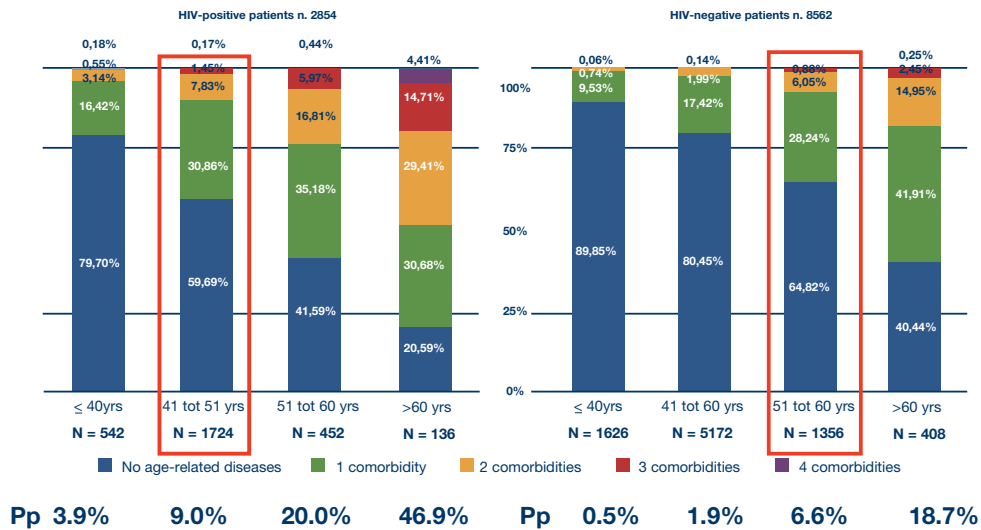
Figure 8. Prevalence of two or more comorbid conditions was higher in HIV-positive cases than in age-, gender-, race-, and region-matched controls in every age group analyzed. (Source: Dr. Giovanni Guaraldi, University of Modena, Italy [58])

similar to the rate in matched HIV-negative 51- to 60-year old controls (9.0% versus 6.6%). Polypathology prevalence in 51-to-60-year-old people with HIV was similar to the rate in HIV-negative controls older than 60 (20.0% versus 18.7%).

Four variables independently predicted polypathology in multivariate logistic regression analysis: every additional year of age (β = 0.11, P < 0.001), every additional year of antiretroviral therapy (β = 0.01, P < 0.001), nadir CD4 count below 200 cells/mm3 (β = 0.87, P < 0.001), and male gender (β = 0.59, P < 0.001).

Guaraldi noted two limitations to this analysis: Sensitivity for detecting comorbidities may have differed in the two groups because the investigators used different methods to detect these conditions in HIV-positive cases and HIV-negative controls. There may be a survival bias, especially in older age groups, because of the cross-sectional nature of the study.

With these limitations in mind, the researchers suggested that polypathology prevalence in people with HIV infection "anticipates" polypathology prevalence in the general population by 10 years. They noted that two important HIV-specific variables—lower nadir CD4 count and longer antiretroviral duration—independently predicted polypathology in this population. On the basis of their findings, Guaraldi and colleagues suggested earlier screening for noninfectious comorbidities is warranted in people with HIV infection.

Age-related comorbidity rates higher in older HIV group than matched controls

Age-related comorbidities, including congestive heart failure, renal failure, and liver disease, were more prevalent in 50-and-older people with HIV than in age- and gender-matched controls in a large database analysis.[59] The 50-and-old HIV group also had higher rates of comorbidities than a gender-matched group of younger adults with HIV.

Ella Nkhoma and GlaxoSmithKline colleagues based this analysis on the Impact National Benchmark Database, a deidentified US healthcare insurance claims database of more than 82 million people cared for since 1997. This study focused on people with continuous follow-up of at least 6 months as of 1 January 2009, including 34,766 HIV-positive people 50 years old or older, 104,298 age- and gender-matched HIV-negative people, and 74,476 gender-matched HIV-positive people from 18 to 49 years old. Everyone in the analysis had full pharmacy benefits.

Three quarters of people (73.6%) in the 50-and-older groups were between 50 and 59, 22.4% were between 60 and 79, and 21.7% were women. In the 50-and-older HIV group, 55.3% had ever taken antiretrovirals, compared with 44.1% of the under-50 HIV group. In the older and younger HIV groups, 15.6% and 15% had a CD4 count under 200 cells/mm3, 53% and 50.5% had a viral load under 400 copies/mL, and 6.2% and 7.9% had a viral load over 100,000 copies/mL.

Comparing 50-and-older HIV-positive people with the 50-and-older HIV-negative group, Nkhoma found higher comorbidity prevalence ratios for

many cardiovascular, metabolic, malignant, and neuropsychiatric diseases (Table 5). The comparison between 50-and-older people with HIV and younger HIV-positive people confirmed higher prevalence ratios for many of these same diseases in the older group (Table 5). In the younger HIV-positive group, only drug abuse was more prevalent than in the older group. The older and younger groups with HIV did not differ in prevalence of psychoses.

Among HIV-positive people in the database with a CD4 count available, nearest CD4 count was below

350 cells/mm3 for patients diagnosed with metastatic cancer, lymphoma, weight loss, and coagulopathy.

Of the coinfections analyzed in 50-or-older people with and without HIV, the HIV/non-HIV prevalence ratio was 15 for HBV, 9.8 for HCV, and 6.4 for herpes simplex virus (HSV). Prevalence of CMV among 50-or-older people with HIV was 1.5%; there were virtually no cases of CMV among similarly aged HIV-uninfected people. Making the same comparison between the older and younger HIV groups, the investigators calculated older/young prevalence

Table 5. Comorbidity prevalence ratios in 50-and-older HIV patients and two comparison groups

Disease	Prevalence ratio (95% CI) for 50+ with HIV versus 50+ without HIV	Prevalence ratio (95% CI) for 50+ with HIV versus 18-49 with HIV
Cardiovascular		
Ischemic heart disease	1.30 (1.26 to 1.32)	2.30 (2.23 to 2.36)
Congestive heart failure	2.28 (2.19 to 2.37)	3.26 (3.11 to 3.42)
Peripheral vascular disease	1.96 (1.87 to 2.06)	4.53 (4.23 to 4.85)
Coagulopathy	4.62 (4.35 to 4.92)	1.86 (1.77 to 1.96)
Stroke	2.36 (2.21 to 2.53)	4.06 (3.74 to 4.43)
Hypertension	1.25 (1.23 to 1.27)	2.22 (2.18 to 2.26)
Hyperlipidemia	1.32 (1.30 to 1.33)	1.50 (1.48 to 1.52)
Metabolic/Bone		
Diabetes	1.48 (1.43 to 1.52)	2.47 (2.38 to 2.55)
Renal failure	4.49 (4.21 to 4.80)	3.00 (2.81 to 3.20)
Liver disease	4.94 (4.72 to 5.17)	1.97 (1.90 to 2.05)
Bone loss/vitamin D deficiency	1.51 (1.47 to 1.56)	2.04 (1.97 to 2.12)
Weight loss	11.0 (8.4 to 14.4)	2.01 (1.69 to 2.38)
Cancer		
Metastatic cancer	2.79 (2.56 to 3.04)	3.11 (2.82 to 3.43)
Tumor (without metastases)	1.92 (1.86 to 2.00)	2.89 (2.76 to 3.01)
Lymphoma	5.53 (5.00 to 6.12)	2.11 (1.94 to 2.30)
Neuropsychiatric/Social		
Depression	2.92 (2.22 to 2.36)	1.07 (1.04 to 1.10)
Alcohol abuse	2.21 (2.05 to 2.38)	1.13 (1.05 to 1.20)
Drug abuse	4.90 (4.49 to 5.34)	0.92 (0.86 to 0.98)
Psychoses	3.19 (2.80 to 3.65)	1.07 (0.96 to 1.20)

Source: Dr. Ella Nkhoma, GlaxoSmithKline, Research Triangle Park, USA .[59]

ratios of 1.2 for HBV, 2.6 for HCV, 0.7 for HSV, and 1.9 for CMV.

Nkhoma noted that the database does not include data on race, disease stage, or HIV transmission route. Because everyone analyzed had full pharmacy benefits and most were younger than 70 years old, the results may not apply to low-income populations or the very elderly. With those caveats in mind, the investigators proposed that "the contrast in prevalence estimates observed support the hypothesis that HIV infection and long-term exposure to combination antiretroviral therapy may lead to accelerated aging in the HIV population resulting in excess age-related morbidity."

Non-AIDS multimorbidity more frequent in IDUs with versus without HIV

Aging-related chronic health conditions proved more prevalent in HIV-positive injection drug users (IDUs) than in HIV-negative IDUs from the same cohort in Baltimore, Maryland.[60] This analysis of the ALIVE cohort also found evidence that a high proportion of these conditions remained undiagnosed and untreated.

Megan Salter (Johns Hopkins Bloomberg School of Public Health) and colleagues planned this study to determine the prevalence of non-AIDS conditions, to identify correlates of increased multimorbidity (simultaneous non-AIDS conditions), and to compare prevalence of clinically identified versus self-reported conditions in HIV-positive and negative members of the ALIVE cohort. ALIVE is an ongoing community-

based cohort that includes adults with a history of injection drug use and a confirmed HIV test. Cohort members have clinical exams and give blood samples every 6 months. Fibroscan for liver fibrosis was added in 2006; spirometry and serum creatinine determinations were added in 2007.

This analysis focused on seven chronic health conditions: obesity (body mass index at or above 30 kg/m2), hypertension (systolic pressure at or above 140 mm Hg, diastolic pressure at or above 90 mm Hg, or self-reported antihypertensive therapy), diabetes (hemoglobin A1c above 6.5% or self-reported diabetes treatment), kidney dysfunction (urine protein-creatinine ratio below 60 mL/min per 1.73 m2), anemia (hemoglobin below 13 g/dL for men and below 12 g/dL for women), liver fibrosis/cirrhosis (stiffness at or above 9.3 kPa on transient elastography or Metavir score at or above F2 or significant fibrosis), and obstructive lung disease (FEV1/FVC below 70% on portable spirometry).

Of the 1262 IDUs studied, 362 (29%) had HIV infection. The HIV-positive and negative groups did not differ significantly in proportion of men (64.1% and 65.4%), proportion homeless in the last 6 months (13.7% and 14.8%), proportion of cigarette smokers in the last 6 months (82.3% and 83.7%), or proportion with depressive symptoms (21.9% and 21.6%). The HIV group had a significantly higher proportion of African Americans (93.4% versus 85.2%) and people never married at baseline (73.5% versus 62.0%) and significantly lower proportions of currently working people (15.0% versus 26.4%) and people with alcohol use in the past 6 months (42.0% versus 54.9%),
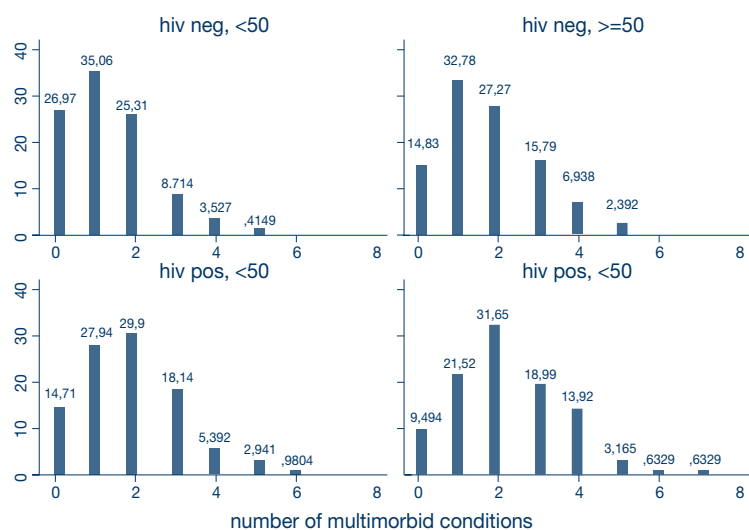

Figure 9. Number of multimorbid conditions differed by HIV status and age among IDUs in the ALIVE cohort in Baltimore. (Source: Dr. Megan Salter, Johns Hopkins Bloomberg School of Public Health, Baltimore. [60])

injection drug use in the last 6 months (33.7% versus 41.7%), and noninjection drug use in the last 6 months (33.1% versus 44.7%).

Among people with HIV infection, a greater percentage of persons with more mulitmorbidities had a CD4 count below 200 cells/mm3 (P = 0.006). But having an undetectable viral load or taking antiretrovirals in the last 6 months had no impact on number of comorbidities in IDUs with HIV.

Proportions of cohort members with none of the seven conditions analyzed were higher among HIV-negative people under 50 than HIV-positive people under 50 (27% versus 15%) and among HIV-negative people over 50 than HIV-positive people over 50 (15% versus 9%) (Figure 9). The under-50 HIV-positive group had higher proportions with two multimorbidities (30% versus 25%), three multimorbidities (18% versus 9%), four multimorbidities (5.3% versus 3.5%), or five multimorbidities (2.9% versus 0.4%) compared with the under-50 HIV-negative group. Compared with HIV-negative IDUs over 50, HIV-positive IDUs over 50 had higher proportions with two multimorbidities (32% versus 27%), three multimorbidities (19% versus 16%), four multimorbidities (14% versus 7%), or five multimorbidities (3.2% versus 2.3%).

Among IDUs with HIV, kidney dysfunction was significantly more prevalent among those 50 and older than in younger people with HIV (54.8% versus 42.9%, P = 0.026). Hypertension was also more prevalent in the older HIV group than in younger IDUs with HIV (46.2% versus 28.9%, P = 0.001), as was obstructive lung disease (23.5% versus 14.7%, P = 0.042). Hypertension was more prevalent in older than younger HIV-negative IDUs (50.5% versus 28.4%, P = 0.000), as was fibrosis/cirrhosis (25.5% versus 11.7%, P = 0.000).

Ordinal logistic regression analysis identified seven independent predictors of increased multimorbidity:

- HIV pos. and >200 CD4 cells/mm3 (vs HIV neg.): *adjusted OR 1.47, P = 0.004*
- HIV pos. and <200 CD4 cells/mm3 (vs HIV neg.): adjusted OR 3.59, P = 0.000
- Every additional year of age: *adjusted OR 1.06, P = 0.000*
- Female gender: *adjusted OR 1.51, P = 0.000*
- Depressive symptoms: *adjusted OR 1.40, P = 0.008*
- Cigarette smoking: *adjusted OR 0.669, P = 0.004*
- Noninjection drug use: *adjusted OR 0.735, P = 0.005*

The researchers suggested that the apparently protective effect of cigarette smoking and noninjection drug use could be explained by lower body mass index and lower blood pressure in smokers or by the "healthy drug user effect." (A healthy drug user effect may occur if IDUs stop using drugs because they are experiencing health problems, while healthier IDUs continue to inject drugs; that could result in a biased association between drug use and better health.)

Among IDUs with HIV who were identified by clinical measures in this study as having kidney disease or liver cirrhosis, 83.8% and 83.9%, respectively, reported never being told by a healthcare worker that they had these conditions. Among HIV-negative IDUs identified by clinical measures in this study as having three conditions, majorities reported never being told they had kidney disease (83%), cirrhosis (85.7%), or obstructive lung disease (53.1%). The investigators proposed that future work should try to identify reasons for this lack of knowledge about important conditions.

Salter and coworkers cautioned that their analysis is limited by missing data on other important non-AIDS health conditions (including cardiovascular disease, cancer, and bone disease). They noted that diabetes may be underestimated in these HIV-positive IDUs because the analysis relied on hemoglobin A1c to detect diabetes.[61] And they suggested their findings may not apply to IDU populations unlike this urban, largely African-American group.

The investigators concluded that HIV infection and advanced immune suppression are associated with a greater number of multimorbidities in IDUs. Although use of combination antiretrovirals was not associated with multiple morbidities in this study, the researchers proposed that further analysis according to antiretroviral class could be revealing.

HIV and Immune Cell Senescence

T-cell senescence linked to persistent KS despite good HIV control

Immunosenescent CD4 and CD8 cells were associated with persistent Kaposi sarcoma (KS) in HIV-positive men with well-controlled HIV replication in a study at the University of California, San Francisco (UCSF).[62] Men with KS also had lower levels of naive CD4 and CD8 cells than a comparison HIV group without KS.

Development of KS in apparently healthy young men was one of the first signals that an epidemic of immunodeficiency disease had begun in the early

1980s. KS emerged as a virtual beacon of low CD4 counts in the early years of the epidemic, but incidence of this previously rare malignancy declined with wide use of triple therapy in the 1990s. Recently, though, UCSF clinicians noted development of classical KS lesions in a small cluster of men responding well to antiretroviral therapy.[63] The UCSF investigators hypothesized that early HIV-associated waning of T-cell function—or immunosenescence—may explain emergence of KS in this population.

Dendritic cell levels similar in young HIV-positives and old HIV-negatives

Levels of plasmacytoid dendritic cells, a key component in immune control of viruses, were as low in 20- to 30-year-olds with HIV as in 50- to 65-year-olds without HIV, according to results of a small comparative study at the University of Medicine and Dentistry of New Jersey (UMDNJ).[64] Dendritic cells from the younger people with HIV produced levels of infection-fighting interferon-α (IFN-α) similar to levels in the older people without HIV.

By producing IFN-α, plasmacytoid dendritic cells affect both the innate and adaptive immune response, noted Jihong Dai and UMDNJ colleagues. Levels of circulating plasmacytoid dendritic cells decrease with age and with progressive HIV infection, and lower levels of these critical immune cells predict opportunistic infection. Plasmacytoid dendritic cell number and function correlate inversely with viral load, and antiretroviral therapy can restore both cell number and function.

Although earlier research demonstrated replicative senescence in the T-cell compartment of people with HIV infection, the impact of HIV and aging on dendritic cells had not been assessed until this study by Dai and colleagues. They hypothesized that premature aging of plasmacytoid dendritic cells occurs during progressive HIV infection.

To test that hypothesis, they compared four groups: (1) 14 young (18- to 30-year-old) people without HIV, (2) 18 young (20- to 30-year-old) people with HIV, (3) 17 older (50- to 65-year-old) people without HIV, and (4) 18 older (50- to 65-year-old) HIV-positive people. Of the 18 people in the young HIV group, 9 had a viral load below 66 copies/mL and a CD4 count above 400 cells/mm3, while 9 had a higher viral load and a lower CD4 count. Of the 18 older people with HIV, 11 had a viral load below 66 copies/mL, 7 had a higher viral load, 10 had a CD4 count above 400 cells/mm3, and 8 had a lower CD4 count.

Using white blood cell counts and FACS analysis, Dai determined that absolute numbers of circulating plasmacytoid dendritic cells decreased with age and with HIV infection and were lowest in the older HIV-positive group (Figure 10). Plasmacytoid dendritic cell numbers in the younger HIV group were virtually the same as numbers in the older HIV-negative group. IFN-α production stimulated by HSV DNA and HIV RNA was lower in older than in younger people, and lower with HIV than without HIV. IFN-α production was lower in young people with HIV than in older people without HIV. Results were similar when Dai and coworkers determined the percentage of IFN-α-producing plasmacytoid dendritic cells.

To determine what accounts for deficient plasmacytoid dendritic cell number and function with HIV and aging, the investigators considered three possibilities: (1) increased maturation of plasmacytoid dendritic cells, possibly as a result of chronic viral stimulation, (2) enhanced turnover of plasmacytoid dendritic cells with HIV infection and aging, and (3) replicative senescence of plasmacytoid dendritic cells.

Using CD40 expression as a marker of dendritic cell maturation, Dai and colleagues found more matured plasmacytoid dendritic cells in HIV groups than in HIV-negative controls. Again, the younger HIV group had more matured plasmacytoid dendritic cells than the older HIV-negative group, a finding suggesting that persisting HIV infection may be related to maturation of dendritic cells.

The UMDNJ team also found a trend toward a higher percentage of Ki67-expressing plasmacytoid dendritic cells (which have been described as newly divided plasmacytoid dendritic cells during acute
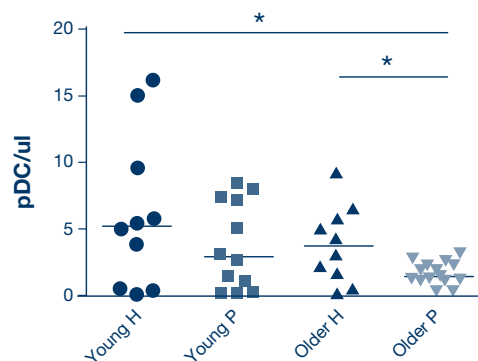

Figure 10. Numbers of plasmacytoid dendritic cells, a key component in viral control, were lower in people with HIV infection than in HIV-negative comparison groups. Dendritic cell numbers in the younger HIV group were lower than in the older control group. H, healthy controls; P, HIV-positives. (Source: Dr. Jihong Dai, University of Medicine and Dentistry of New Jersey, USA [64])

SIV infection) in both HIV-positive and aged healthy individuals. That finding, they proposed, implies accelerated turnover of plasmacytoid dendritic cells in both the HIV-infected group and the older control group. Finally, Dai and coworkers used a three-color flow-Fish assay to record a shorter telomere length in plasmacytoid dendritic cells from the two older groups and the younger HIV group than in the young HIV-negative group, a result indicating increased telomere shortening with age and HIV infection. At the time of this presentation, Dai had analyzed telomere length in only 1 young person with HIV.

These analyses did not control for numerous factors that may affect plasmacytoid dendritic cell number and function. Still, considering all these findings, Dai and colleagues proposed that they "support the hypothesis that there is an accelerated senescence, possibly driven by chronic immune activation, in circulating plasmacytoid dendritic cells from HIV-infected individuals."

Lopinavir/ritonavir could trigger premature aging in coronary endothelial cells

Cell-culture studies and ex vivo analysis of peripheral blood mononuclear cells (PBMCs) from people with HIV infection yielded evidence that long-term exposure to ritonavir or ritonavir-boosted lopinavir may induce premature aging in coronary artery endothelial cells and PBMCs.[65] Statins and antioxidants reversed or prevented PI-induced senescence, oxidative stress, and inflammation in these experiments by Jacqueline Capeau (Université Pierre et Marie Curie and INSERM) and colleagues.
Numerous studies in people with HIV infection link PI use to premature cardiovascular disease through endothelial dysfunction, Capeau noted, either indirectly via dyslipidemia or directly by altering endothelial cells. The investigators hypothesized that premature cardiovascular disease may also result from accelerated cell aging caused by HIV infection, antiretroviral therapy, or both. In older people without HIV, prelamin A accumulates in vascular smooth muscle cells, which also express senescence markers.

To assess the impact of proatherogenic PIs—ritonavir and lopinavir/ritonavir—on these factors, Capeau and coworkers planned a series of experiments with several goals. First they aimed to determine whether long-term (30-day) exposure to ritonavir (7.5 µM) or lopinavir/ritonavir (10/2 µM) could induce accelerated senescence of human vascular coronary endothelial cells in primary culture. PI exposure progressively and significantly decreased cell proliferation and replication compared with cells not exposed to

the PIs. Exposure to ritonavir or lopinavir/ritonavir significantly increased expression of two cell-cycle arrest proteins, p21 and p53, and of senescence-associated β-galactosidase activity. The PIs also induced prelamin A accumulation and structural nuclear abnormalities.

The second goal was to search for senescence markers in PBMCs from HIV-positive people taking ritonavir-boosted PIs. PBMCs from people taking ritonavir-boosted PIs expressed prelamin A and the senescence markers p21 and p53, whereas PBMCs from patients taking only nucleosides did not.

The third goal was to determine whether endothelial cells exposed to the PIs had increased oxidative stress and inflammation. Both ritonavir and lopinavir/ritonavir significantly increased reactive oxygen species and levels of three inflammation markers (interleukin 6, interleukin 8, and MCP-1) in endothelial cells compared with cells not exposed to these PIs.

The fourth goal was to assess whether pravastatin or FTI-277 (a farnesyltransferase inhibitor) improves these PI-induced effects in endothelial cells. Both agents decreased levels of farnesylated prelamin A and blocked expression of p21 and p53 in endothelial cells. Pravastatin or FTI-277 also reversed oxidative stress and significantly lowered levels of the inflammation markers interleukin 6, interleukin 8, and MCP-1.

The fifth goal was to determine whether senescence markers in PBMCs of patients taking ritonavir-boosted PIs were affected if the patients were also treated with a statin. Statins did decrease expression of p21 and p53 in these cells.

The sixth goal was to determine whether antioxidants improve observed PI-induced adverse effects in endothelial cells. Two antioxidants, N-acetyl cysteine and Mn-TBAP, had no impact on prelamin A accumulation. But both antioxidants did prevent oxidative stress, senescence, and inflammation as indicated by markers of those activities in antioxidant-exposed cells.

Capeau and colleagues concluded that ritonavir and lopinavir/ritonavir "trigger premature senescence, oxidative stress, and inflammation in human endothelial cells by a mechanism involving prelamin A accumulation." Those findings, they proposed, suggest that ritonavir-boosted PIs may contribute to early development of cardiovascular disease in PI-treated patients. Statins, the researchers suggested, could benefit PI-treated patients by reversing PI-induced vascular senescence.

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VERKORTE PRODUCTINFORMATIE
ISENTRESS 400 mg filmomhulde tabletten.

Samenstelling

Filmomhulde tablet: 400 mg raltegravir (als kaliumzout).

Indicaties

ISENTRESS is geïndiceerd in combinatie met andere antiretrovirale geneesmiddelen voor de behandeling van humaan-immunodeficiëntievirus (hiv-1)-infectie bij volwassen patiënten. Deze indicatie is gebaseerd op gegevens over veiligheid en werkzaamheid uit twee dubbelblinde, placebogecontroleerde onderzoeken bij eerder behandelde patiënten en een dubbelblind, met werkzame stof gecontroleerd onderzoek bij niet eerder behandelde patiënten.

Klinische ervaring

Bewijs voor de effectiviteit van ISENTRESS is gebaseerd op analyses van 96-weeksdata uit twee lopende, gerandomiseerde, dubbelblinde, placebogecontroleerde studies (BENCHMRK 1 en BENCHMRK 2, Protocols 018 en 019) bij eerder met antiretrovirale middelen behandelde, met hiv-1 geïnfecteerde volwassen patiënten, en analyse van 96-weeksdata uit een lopende, gerandomiseerde, dubbelblinde, met werkzame stof gecontroleerde studie (STARTMRK, Protocol 021) bij niet eerder met antiretrovirale middelen behandelde en met hiv-1 geïnfecteerde volwassen patiënten. **Contra-indicaties** Overgevoeligheid voor het werkzame bestanddeel of voor één van de hulpstoffen.

Waarschuwingen en voorzorgen

In het algemeen werd in de farmacokinetiek van raltegravir aanzienlijke inter- en intra-individuele variabiliteit waargenomen.

Raltegravir heeft een relatief lage genetische barrière voor resistentie. Daarom moet raltegravir waar mogelijk gecombineerd worden met twee andere actieve ARTs om de kans op virologisch falen en het optreden van resistentie te beperken.

Bij niet eerder behandelde patiënten zijn de klinische gegevens over gebruik van raltegravir beperkt tot gebruik in combinatie met twee nucleotide-reverse-transcriptaseremmers (NRTIs) (emtricitabine en tenofovirdisoproxilfumaraat).

De veiligheid en werkzaamheid van ISENTRESS zijn niet vastgesteld bij patiënten met ernstige onderliggende leveraandoeningen. Daarom moet ISENTRESS bij patiënten met een ernstige leverfunctiestoornis met voorzichtigheid worden toegepast. Patiënten met een al eerder bestaande leverfunctiestoornis waaronder chronische hepatitis hebben tijdens antiretrovirale combinatietherapie een verhoogde frequentie van leverfunctiestoornissen gehad en moeten volgens de standaardpraktijk worden gecontroleerd.

Er zijn zeer beperkte gegevens over het gebruik van raltegravir bij patiënten die naast hiv ook geïnfecteerd zijn met hepatitis B-virus (HBV) of hepatitis C-virus (HCV). Patiënten met chronische hepatitis B of C die worden behandeld met antiretrovirale combinatietherapie hebben een hogere kans op ernstige en mogelijk fatale leverbijwerkingen.

Voorzichtigheid moet worden betracht bij gelijktijdige toediening van ISENTRESS met sterke inductoren van uridinedifosfaat-glucuronosyltransferase (UGT) 1A1 (bijvoorbeeld rifampicine). Rifampicine verlaagt de plasmaconcentraties van raltegravir, de invloed daarvan op de werkzaamheid van raltegravir is onbekend. Maar als gelijktijdige toediening met rifampicine onontkoombaar is, kan verdubbeling van de dosis ISENTRESS worden overwogen.

Myopathie en rabdomyolyse zijn gemeld, maar het verband daarvan met ISENTRESS is onbekend. Gebruik met voorzichtigheid bij patiënten die in het verleden myopathie of rabdomyolyse hebben gehad of anderszins gepredisponeerd zijn.

Huiduitslag kwam bij eerder behandelde patiënten die een behandeling met ISENTRESS + darunavir kregen vaker voor dan bij patiënten die ISENTRESS zonder darunavir of darunavir zonder ISENTRESS kregen.

ISENTRESS bevat lactose. Patiënten met zeldzame erfelijke stoornissen als galactose-intolerantie, Lapp-lactasedeficiëntie of glucose-galactosemalabsorptie mogen dit geneesmiddel niet gebruiken.

Interacties

Uit in-vitro-onderzoek blijkt dat raltegravir geen substraat van cytochroom P450 (CYP)-enzymen, is, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 of CYP3A niet remt geen inductie van CYP3A4 geeft en het door P-glycoproteïne gereguleerde transport niet remt. Op basis van deze gegevens wordt niet verwacht dat ISENTRESS de farmacokinetiek beïnvloedt van geneesmiddelen die substraten zijn van deze enzymen of P-glycoproteïne.

Op basis van in vitro- en in-vivo-onderzoeken wordt raltegravir voornamelijk uitgescheiden door metabolisme via UGT1A1-geïnduceerde glucuronidatieroute.

Hoewel uit in-vitro-onderzoek gebleken is dat raltegravir geen remmer is van de UDP-glucuronosyltransferases (UGTs) 1A1 en 2B7, doet één klinisch onderzoek op grond van een waargenomen effect op de glucuronidatie van bilirubine vermoeden dat er in vivo enige remming van UGT1A1 kan voorkomen. Maar de omvang van het effect leidt waarschijnlijk niet tot klinisch belangrijke geneesmiddelinteracties.

Bijwerkingen

Bijwerkingen waarbij er volgens de onderzoekers een causaal verband was (alleen of in combinatie met andere ART) worden hieronder per frequentie opgesomd.

Vaak: abnormaal dromen, slapeloosheid, duizeligheid, hoofdpijn, vertigo, opgezwollen buik, buikpijn, diarree, winderigheid, misselijkheid, braken, huiduitslag, asthenie, vermoeidheid, pyrexie, verhoogd alanineaminotransferase, atypische lymfocyten, verhoogd aspartaataminotransferase, verhoogde triglyceriden in het bloed, verhoogde lipase.

Soms: genitale herpes, folliculitis, gastro-enteritis, herpes simplex, infectie met herpesvirus, herpes zoster, influenza, molluscum contagiosum, nasofaryngitis, bovensteluchtweginfectie, huidpapilloom, anemie, anemie wegens ijzergebrek, pijn in lymfeklieren, lymfadenopathie, neutropenie, immuunreconstitutiesyndroom, geneesmiddelenovergevoeligheid, overgevoeligheid, anorexia, cachexie, verminderde eetlust, diabetes mellitus, dyslipidemie, hypercholesterolemie, hyperglykemie, hyperlipidemie, hyperfagie, meer eetlust, polydipsie, psychische aandoening, zelfmoordpoging, angst, verwarring, neerslachtige stemming, depressie, ernstige depressie, slapeloosheid in het midden van de nacht, wisselende stemming, nachtmerrie, paniekaanval, slaapstoornis, amnesie, carpaaltunnelsyndroom, cognitieve stoornis, aandachtsstoornis, duizeligheid bij houdingsverandering, dysgeusie, hypersomnie, hypo-esthesie, lethargie, geheugenstoornis, migraine, perifere neuropathie, paresthesie, slaperigheid, spanningshoofdpijn, tremoren, visusverslechtering, tinnitus, palpitaties, sinusbradycardie, ventriculaire extrasystoles, opvliegers, hypertensie, dysfonie, epitaxis, neusverstopping, gastritis, last van de buik, pijn in de bovenbuik, gevoeligheid van de buik, pijn in de anus of van het rectum, obstipatie, droge mond, dyspepsie, erosieve duodenitis, oprispingen, gastro-oesofageale reflux, gingivitis, glossitis, odynofagie, acute pancreatitis, maagzweer, rectale bloeding, hepatitis, hepatische steatose, acné, alopecia, dermatitis acneiforme, droge huid, erytheem, ingevallen gezicht, hyperhidrose, verkregen lipodystrofie, lipohypertrofie, nachtelijk zweten, prurigo, pruritus, gegeneraliseerde pruritus, maculaire uitslag, maculopapulaire uitslag, uitslag bij pruritus, huidlaesie, urticaria, xeroderma, artralgie, artritis, rugpijn, pijn in de flank, musculoskeletale pijn, myalgie, nekpijn, osteopenie, pijn in de extremiteiten, tendinitis, nierfalen, nefritis, nefrolithiase, nycturie, niercyste, nierfunctiestoornis, tubulo-interstitiële nefritis, erectiestoornis, gynaecomastie, menopauzale verschijnselen, pijn op de borst, rillingen, oedeem in het gezicht, meer vetweefsel, zich schrikachtig voelen, malaise, perifeer oedeem. verlaagde absolute neutrofiele telling, verhoogde alkalische fosfatase, verlaagd bloedalbumine, verhoogde bloedamylase, verhoogd bloedbilirubine, verhoogd bloedcholesterol, verhoogd bloedcreatine, verhoogd bloedglucose, verhoogd BUN, verhoogde creatinefosfokinase, nuchter bloedglucose verhoogd, glucose aanwezig in urine, verhoogd HDL, verlaagd LDL, verhoogd LDL, minder trombocyten, positief op rode bloedcellen in urine, grotere tailleomtrek, gewichtstoename, minder witte bloedcellen, onbedoelde overdosis.

Niet bekend: suïcidale gedachten, suïcidaal gedrag (vooral bij patiënten met een voorgeschiedenis van psychische aandoeningen), *Stevens Johnson syndroom.*

Patiënten die tevens geïnfecteerd zijn met het hepatitis B- en/of hepatitis C-virus

In fase III-onderzoeken mochten eerder behandelde patiënten (N = 114/699 ofwel 16 %; HBV=6 %, HCV=9 %, HBV+HCV=1 %) en niet eerder behandelde patiënten (N = 34/563 of 6 %; HBV=4 %, HCV=2 %, HBV+HCV=0,2 % met gelijktijdige chronische (maar geen acute) infectie met hepatitis B en/of hepatitis C) meedoen op voorwaarde dat de leverfunctietests bij baseline niet hoger waren dan 5 keer de normale bovengrens. In het algemeen was het veiligheidsprofiel van ISENTRESS bij patiënten met een gelijktijdige infectie met hepatitis B-en/of hepatitis C-virus gelijk aan die van patiënten zonder hepatitis B-en/of hepatitis C-virus, hoewel in beide behandelingsgroepen de frequentie van AST- en ALT-afwijkingen in de subgroep met gelijktijdige infectie met hepatitis B en/of hepatitis C iets hoger was. Bij eerder behandelde patiënten traden laboratoriumafwijkingen graad 2 of hoger die een verslechteringsgraad t.o.v. baseline vertegenwoordigen van het AST, ALT of totaal bilirubine op bij respectievelijk 29 %, 34 % en 13 % van met ISENTRESS behandelde gecoïnfecteerde proefpersonen tegen respectievelijk 11 %, 10 % en 9 % van alle andere met ISENTRESS behandelde proefpersonen. Bij niet eerder behandelde patiënten traden laboratoriumafwijkingen graad 2 of hoger die een verslechteringsgraad t.o.v. baseline vertegenwoordigen van het AST, ALT of totaal bilirubine op bij respectievelijk 17 %, 28 % en 17 % van met ISENTRESS behandelde gecoïnfecteerde proefpersonen in vergelijking met respectievelijk 6 %, 6 % en 3 % van alle andere met ISENTRESS behandelde proefpersonen.

Farmacotherapeutische categorie

Antiviraal middel voor systemisch gebruik, Andere antiretrovirale middelen, ATC-code: J05AX08

Afleverstatus

UR

Verpakking

ISENTRESS 400 mg is verkrijgbaar in flesjes met 60 tabletten.

Vergoeding en prijzen

ISENTRESS 400 mg wordt volledig vergoed. Voor prijzen: zie ZI-index.

Raadpleeg de volledige productinformatie (SPC) alvorens ISENTRESS voor te schrijven.

Maart 2010.

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Workshops 2011

1st International Workshop on HIV & Women - *from Adolescence through Menopause*
10 - 11 January 2011 – Washington DC, USA

9th European Workshop on HIV & Hepatitis - Treatment Strategies & Antiviral Drug Resistance
23 - 25 March 2011 – Paphos, Cyprus

12th International Workshop on Clinical Pharmacology of HIV Therapy
13 -15 April 2011 – Miami FL, USA

5th International Workshop on HIV Treatment, Pathogenesis & Prevention Research in Resource Limited Settings (INTEREST)
10 - 13 May 2011 - Dar es Salaam, Tanzania

7th International Workshop on HIV and Hepatitis Co-infection
1 - 3 June 2011 – Milan, Italy

6th International Workshop on Clinical Pharmacology of Hepatitis Therapy
22 - 23 June 2011 – Boston MA, USA

6th International Workshop on Hepatitis C – Resistance & New Compounds
23 - 24 June 2011 – Boston MA, USA

6th International Workshop on HIV Transmission – Principles of Intervention
14 - 15 July 2011 – Rome, Italy

3rd International Workshop on HIV Pediatrics
15 - 16 July 2011 – Rome, Italy

4th International Workshop on Clinical Pharmacology of Tuberculosis Drugs
16 September 2011 – Chicago IL - USA

2nd International Workshop on HIV & Aging
27 - 28 October 2011 – Baltimore MD, USA

2nd International Workshop on XMRV
November 2011 – USA