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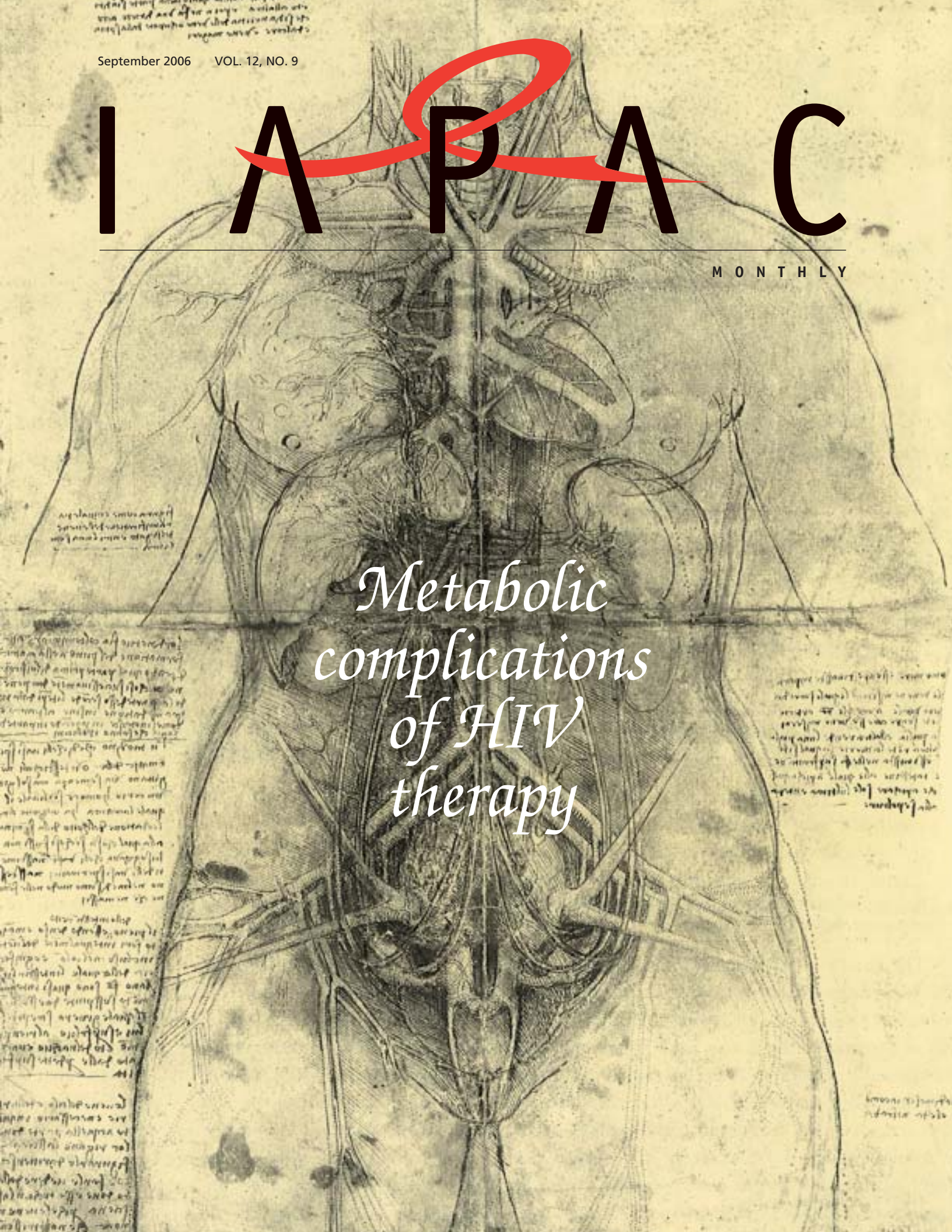

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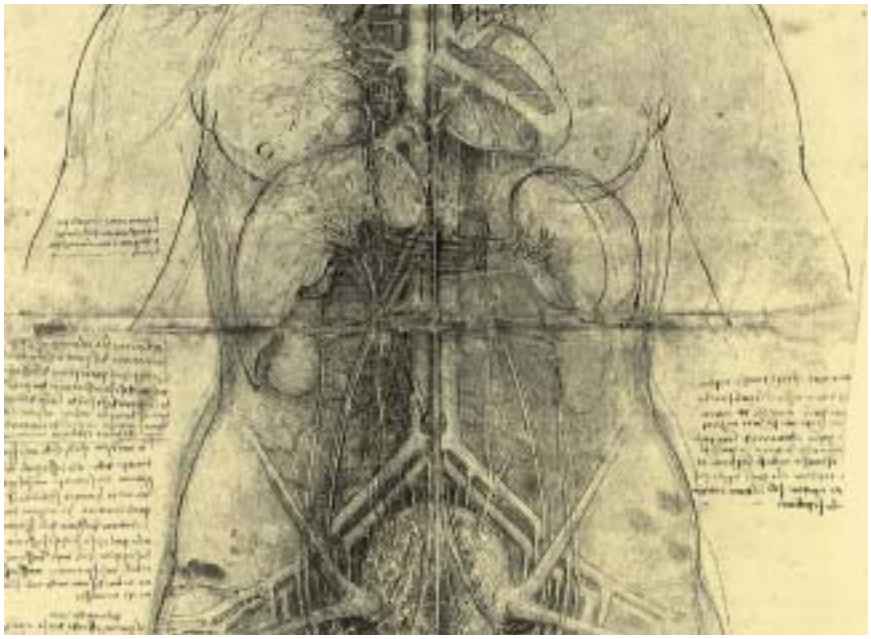

Metabolic complications of HIV therapy

Dominic Chow, Larry Day, Scott Souza, and Cecilia Shikuma

The use of effective antiretroviral therapy (ART) has resulted in tremendous improvements in morbidity and mortality in HIV-positive patients, but the widespread use of effective ART has coincided with increasing reports of metabolic complications. Dominic Chow, Larry Day, Scott Souza, and Cecilia Shikuma report on the management of patients experiencing these complications.

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REPORT FROM THE PRESIDENT

There's something about Galen

José M. Zuniga

During a recent presentation to a group of managed care professionals about next year's introduction in the United States of the proctored GALEN Certification Examination (a developing world-specific version of which the International Association of Physicians in AIDS Care [IAPAC] has administered in southern Africa for the past two years), I was asked to explain "GALEN" as an acronym. As regular readers of the *IAPAC Monthly* know well, the acronym stands for Global AIDS Learning & Evaluation Network. But beyond that literal description, there is a more profound connection behind our branding: its direct association to Claudius Galenus of Pergamum, better known in English as Galen.

Galen was an ancient Greek physician whose views dominated European medicine for over 1,000 years. His *On the Elements According to Hippocrates* describes the philosopher's system of four bodily humors—blood, yellow bile, black bile, and phlegm—which were identified with the four classical elements, and in turn with the seasons. Galen created his own theories from those principles, and much of his work can be seen as building on the Hippocratic theories of the body.

It is difficult to overstate the importance of Galen for European medical thought in the centuries between the fall of Rome and modern times. His collected works total 22 volumes. In his prolific writing, he absorbed all preceding medical thought and shaped the categories within which his successors thought about not only the history of medicine, but its practice as well.

Galen's importance in the history of medicine makes him a particularly appropriate point of reference for IAPAC's GALEN. As the historical Galen collected and codified existing knowledge and developed new theories, methods, and classifications, the IAPAC physician-members who created GALEN have identified the most essential and cutting-edge knowledge for HIV/AIDS-treating physicians and presented that information as a proctored examination. As Galen was emblematic of the movement to systematize the practice of medicine for the good of physicians and their patients, GALEN will systematize the training in and practice of HIV medicine, and create a global standard for defining what it means to become and remain an HIV specialist. It is not an overstatement to assert that the proctored GALEN Certification Examination and its accompanying continuing education offerings will positively impact the field of HIV medicine in developed and developing world countries alike.

In the past few months, IAPAC has fine-tuned GALEN to better meet its objectives. In the developing world, emphasis has been placed upon the benefit to physicians and patients of rigorously enforced standards of care. As agreed upon during a June 2004 World Health Organization (WHO) consultation on the topic of HIV service delivery,[1] training and certification of health workers can perform several important functions, including:

- **Quality assurance.** Transparent and controlled certification procedures help to establish and demonstrate that individual health workers are equipped to perform their tasks. The presence of certified staff is often a standard used in assessing the quality of a service delivery point.
- **Benchmarking.** Clearly defined certification standards help to establish what competencies are expected from health workers, and can give training providers guidance in developing their courses with clear aims and standards in mind.
- **Incentive.** Being rewarded with certification provides an incentive for health workers to attain these standard levels of competence—particularly if such certification is linked to professional progression and/or advantages.
- **Driving change.** The definition of certification standards can in itself be used as an instrument for policy change—for example, in driving the acceptance by professionals (and paraprofessionals) of task shifting between various types of health workers.

In the developed world, GALEN Certification Committee Co-Chair, John G. Bartlett (Johns Hopkins University, Baltimore), has identified several vital benefits to being recognized as an HIV specialist through the GALEN Certification Examination:

- The secured examination will verify clinical competence and certify HIV care expertise based on a standard process.
- The examination will target the body of information that a clinician caring for HIV-positive patients can reasonably be expected to know, with categories weighted by their importance in real-world care (eg, 50% of questions are devoted to overall antiretroviral therapy delivery).
- The examination will be psychometrically analyzed to ensure questions adequately measure knowledge and its application (50% of questions are knowledge-based, and the remaining 50% are case study-based). Authorities in the field of HIV medicine will review the examination to determine the overall quality and clinical relevance of each question.

- Study guides will be written to aid participants in preparing for the examination. The act of preparing for the examination through concentrated study is of immediate benefit to both physicians and patients.
- The examination process will follow established testing standards set by certification boards such as the ABIM, and will be jointly sponsored with equitable contributions by like-minded professional and specialty medical societies. In recognition of the potential ethical problems inherent in associations certifying their own members, IAPAC will establish an independent HIV medicine-specific certification board comprised of relevant professional and specialty medical societies to administer the GALEN Certification Examination and to evaluate its results.

It should be noted that IAPAC has for several years publicly supported efforts by national medical societies in various developed world countries to recognize HIV medicine as a specialized field of study and practice. For example, in the United States, IAPAC endorsed attempts by the HIV Medicine Association (HIVMA) to convince the ABIM and other boards that comprise the American Board of Medical Specialties (ABMS) to approve a "Certificate of Added Qualification (CAQ) in HIV Medicine." This would have allowed primary care physicians to be certified in HIV medicine by taking one year of clinical training and passing a proctored certification examination. However, in July 2006 the ABIM effectively shut down this effort by voting to discontinue the granting of CAQs.[2]

IAPAC continues to support HIVMA as it attempts to push for the creation of an HIV subspecialty through means that would "provide a pathway for future internists and others to receive training and become certified in HIV medicine."[3] But in the meantime, it is our belief that the issue of ensuring quality HIV/AIDS care is too important to allow ABIM's refusal to stand as the last word. We can not indefinitely mark time while there remains a critical need to "acknowledge and to validate the expertise that scores of internists currently practicing on the front-line[s] of HIV medicine now possess."[3]

We have known for some time that providing quality care requires quality training. According to a 1999 study by the Society of General Internal Medicine's AIDS Task Force, "optimal care of HIV infection requires a combination of disease-specific expertise and primary care skills and organization."[4] The study's abstract goes on to note that the "management of HIV has become sufficiently complex that primary care physicians cannot be routinely expected to have extensive specialized knowledge in this area." If such an observation was true seven years ago, how much more urgent is specialized training today? And if training is in fact the answer to the question of how we improve care, then a corollary is that certification is essential to ensure that training is hitting its mark.

Finally, the benefits of effective training and certification resonate beyond the improved capabilities of the individual physician and the improved outcomes for the individual patient. The concept of "disease management" emphasizes the use of integrative care to control or prevent chronic disease and reduce health care costs. Certification can be a cornerstone in the disease management process by assuring that physicians are adequately trained in providing timely and appropriate evidence-based treatment. In a time of scarce human and financial resources, it is imperative that we wisely budget a small portion of our precious time and energy to creating and administering a program that will benefit both patient care and the financial efficiency of our health care systems. ■

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care, and Editor-in-Chief of the IAPAC Monthly.

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Adherence to NNRTI-based regimens less demanding?

Derek Thaczuk

Nonnucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral regimens may successfully control viral load at adherence levels significantly lower than 95%, according to a study and editorial e-published in the October 1, 2006, issue of *Clinical Infectious Diseases*.[1,2]

A widely cited 2000 study showed that the success rates of triple-drug regimens based on protease inhibitors (PIs) dropped off sharply for adherence rates less than 95%. On the strength of this and similar studies, 95% or better adherence has been generally cited as necessary for continued treatment success.

The 2006 study, however, used combinations of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a single PI, without the use of ritonavir (RTV) to boost PI levels. Since that time, NNRTIs and boosted PIs have become more commonly used. New data now suggest that NNRTI-based regimens can be successful even at considerably lower rates of adherence.

David R. Bangsberg (University of California, San Francisco) and colleagues have been studying a group of homeless or marginally housed HIV-positive adults, a group that would be expected to have serious challenges with adherence. The researchers found that most of the PI-treated patients had viral loads of less than 400 copies/mL only at adherence levels of 95% or better, consistent with earlier findings. However, the majority of NNRTI-treated patients had viral loads below 400 copies/mL at adherence rates of above 54%. More of the NNRTI-treated group achieved viral suppression overall, and NNRTIs performed significantly better for those in the 54% to 73% adherence range.

The group of 330 HIV-positive adults, known as the Research on Access to Care in the Homeless (REACH) cohort, were enrolled from San Francisco homeless shelters, meal programs, and low-income hotels between July 1996 and April 2000. Of these individuals, 110 are included in the current published study; 56 receiving PIs, and 54 NNRTIs. All had a median of 14 months of prior antiretroviral therapy including NRTIs, but were receiving their first PI or NNRTI. In the PI-treated group, the drugs in use were nelfinavir (NFV) (64%), indinavir (IDV) (27%), saquinavir (SQV) (7%), and RTV (2%); the NNRTIs were nevirapine (NVP) (62%) and efavirenz (EFV) (38%). The NNRTI and PI groups had similar baseline characteristics. The study was not randomized.

Participants were followed over a median of 9.1 months. Blood draws were done monthly; viral load suppression was defined as "less than 400 copies/mL" so that results could be directly compared to earlier studies.

The average rate of adherence in the study group overall was 70%. To measure adherence, all participants were subject to unannounced pill counts: unscheduled visits were made every three to six weeks, at which antiretroviral drugs were counted. (Unannounced visits make it less likely for participants to "cheat" by dumping unused medications.) Participants could choose to use pill organizers; for those who did not, electronic pill bottle caps (MEMS) were used as another measure of adherence. Participants were divided into adherence rate quartiles (0% to 53%, 54% to 73%, 74% to 94%, and 95% to 100%) with roughly equal numbers in each group.

These published results now confirm earlier reports from this study that moderate adherence to NNRTIs was more likely to lead to viral suppression than comparable adherence to PIs. Response rates at either end of the adherence scale were unsurprising, with the best viral load suppression seen at adherence rates of 95% or above, and the poorest at rates at 53% or below. Significant differences, however, showed up in the intermediate ranges. In particular, for adherence between 54% and 73%, response to NNRTIs was dramatically better than that to PIs ($P = 0.02$).

Similar results were seen in a recent study that found that adherence to NNRTI regimens of above 75% led to sustained viral load suppression, while rates of above 85% were needed with PIs. Neither this study nor Bangsberg's study looked at combinations based on RTV-boosted PIs, or newer PIs such as atazanavir (ATV); the outcome of moderate adherence to these more potent PI-based regimens is still unknown.

These studies indicate that NNRTI-based regimens may be more "forgiving," meaning they may tolerate poorer adherence than previously believed. This is reassuring in real-world situations where near-perfect adherence standards are difficult to meet. However, as Bangsberg states, "reduced disease progression and mortality improves with every increase in adherence level… these data do not alter the goal to achieve the highest level of adherence possible." ■

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Severe immune suppression, poorer CD4 response, successful HAART

Adam Legge

HIV-positive patients who have had very low CD4 counts in the past, even if they now have complete viral suppression due to the use of antiretroviral therapy, have significantly weaker immune responses, according to a brief report in the August 15, 2006, issue of the *Journal of Infectious Diseases*.

Although antiretroviral therapy has significantly improved the prognosis of HIV-positive patients, the recovery of CD4 cells depends on when therapy is started and how long it has continued. Very low CD4 counts may be associated with immune defects that are hard to correct. Those patients with the lowest CD4 counts may not recover CD4 cells to the point of stopping prophylactic drugs.

But the exact relationship between the CD4 nadir and the strength of a patient's immune response after therapy is not clear. Researchers thus designed a study involving 84 HIV-positive patients. All were receiving antiretroviral therapy and all had undetectable viral loads for at least three months. There was a wide range of CD4 nadirs. For this analysis, researchers divided the participants into two groups: those whose CD4 nadir was 200 cells/mm^3 and under, and those whose CD4 nadir was over 200 cells/mm^3. They then compared the strength of the patient's immune response after successful therapy in two ways: the strength of CD4 response to therapy and the CD8 response.

The researchers confirmed that there is a very significant relationship between CD4 nadirs and current CD4 counts. Those whose lowest CD4 count dropped below 200 cells/mm^3 tended to have lower CD4 counts after therapy. But they also found that those with the lowest CD4 nadirs had a weaker immune response, regardless of their post-therapy CD4 count. This suggests that those patients whose CD4 counts drop to very low levels before therapy may not have a completely reconstituted immune response even if their CD4 counts recover. But the researchers stress that there is no cut-off value below which immune responses cannot recover and above which they can. Their results also suggest that the longer a patient is on therapy, the stronger the immune response becomes, contradicting other studies that suggest that the CD4 count eventually reaches a plateau after five to six years of therapy.

Although a low CD4 nadir may mean immune responses are weaker after therapy, prolonged therapy helps even in patients whose CD4 counts dropped below 200 cells/mm^3. These new data also suggest that it may be appropriate to recruit those with low CD4 nadirs into trials of therapeutic vaccines. ■

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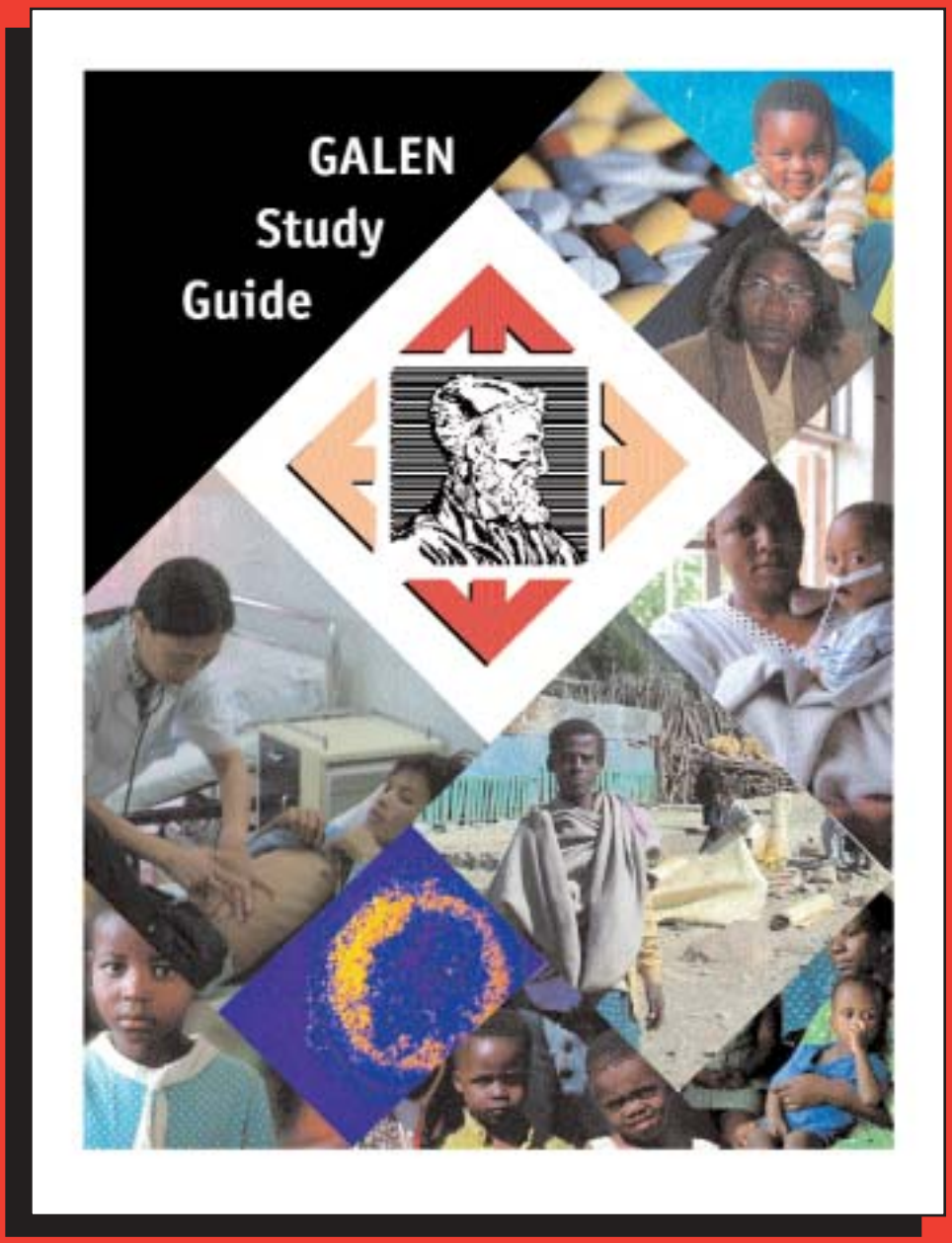

The *GALEN Study Guide* features 100 multiple-choice, best-answer format questions similar to those that make up the GALEN Certification Examination. The study guide includes answer rationale and a sample examination bubble-sheet so that clinicians interested in writing the GALEN Certification Examination may self-assess their knowledge in the 12 areas of HIV medicine covered by the examination.

Produced in collaboration with the US National Institutes of Health (NIH), the GALEN Study Guide is a useful tool to measure and strengthen clinicians' ability to pass the GALEN Certification Examination with a score of 70% or better. Visit www.iapac.org to order your GALEN Study Guide today!

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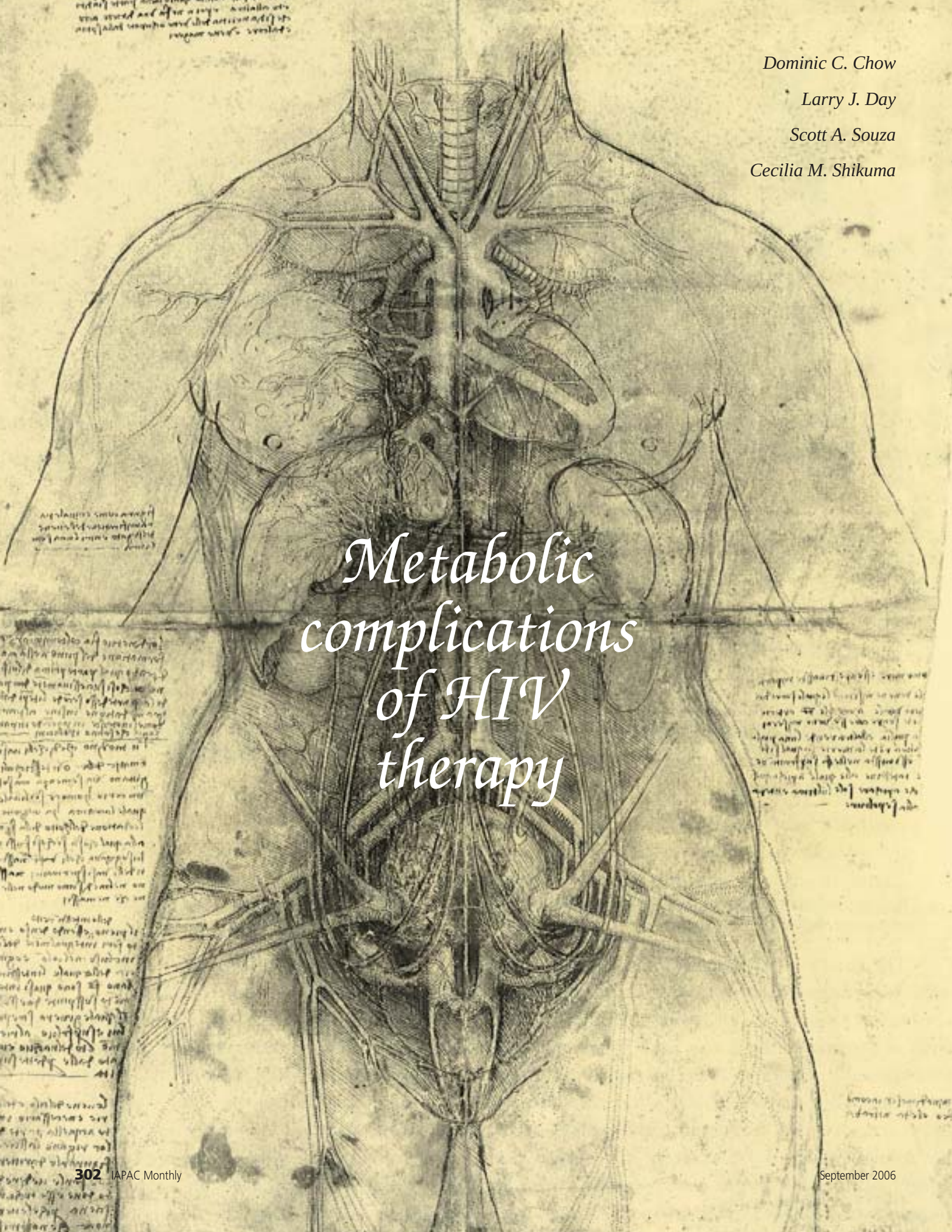
Metabolic complications of HIV therapy



The use of effective antiretroviral therapy (ART) has resulted in tremendous improvements in morbidity and mortality in HIV-positive patients. However, the widespread use of effective ART has coincided with increasing reports of metabolic abnormalities such as impaired glucose metabolism and insulin resistance, lactic acidosis, osteopenia, and dyslipidemia. Distressing morphologic changes in body habitus associated with these metabolic abnormalities are characterized by accumulation of fat in the abdomen (visceral fat compartment) and in the dorsocervical area of the neck, as well as by the depletion of fat in the face, buttocks, and extremities. As the metabolic alterations coinciding with the availability of effective ART are similar to the features seen in the metabolic syndrome ("syndrome X"), one of the major concerns has been the potential for increased cardiovascular morbidity and mortality in this cohort.

The causes of the metabolic disturbances and morphologic changes related to ART are not understood completely. The etiology is likely to involve the effect of HIV per se as well as the direct and indirect effects of ART, superimposed on individual characteristics such as genetic predisposition, gender, and age. There are likely to be both drug class-specific and drug-specific differences in the tendency of antiretroviral medications to cause these effects. Furthermore, although some of the metabolic disturbances may be linked to one another, the interconnections among these metabolic abnormalities have yet to be elucidated. Table 1 summarizes the metabolic and morphologic complications associated with HIV infection and ART.

HIV-Associated Lipodystrophy

Background and definition

Body fat abnormalities are common in patients receiving potent ART, occurring in 30% to 50% or more of participants in several large, prospective studies.[1-6] These abnormalities have been reported to include, singularly or in combination, central fat accumulation, evidenced by increased abdominal girth (due to increase in visceral fat); development of a dorsocervical fat pad ("buffalo hump"); and breast enlargement, as well as loss of peripheral subcutaneous fat (lipoatrophy). The latter designation includes subcutaneous fat loss of the extremities, buttocks, and face. The combination of these morphologic changes and antiretroviral-associated metabolic derangements has been referred to as the lipodystrophy syndrome (Figures 1-4). The lipodystrophy syndrome is distressing to HIV-positive patients on ART and has been linked with both short-term and long-term failure to comply with antiretroviral regimens.[7,8] In addition, both the fat accumulation component and the fat depletion component of the syndrome are associated with substantial metabolic dysregulation that may have an impact on long-term cardiovascular morbidity and mortality in HIV-positive patients.

Table 1. **Metabolic and morphologic complications associated with HIV infection and ART**

Morphologic changes
Adipose accumulation
• Abdominal (visceral) adiposity
• Dorsocervical fat enlargement
• Breast enlargement
Lipoatrophy
• Extremities
• Face
• Buttocks
Metabolic disturbances
Glucose metabolism
• Insulin resistance
• Impaired glucose tolerance
• Diabetes mellitus
Dyslipidemia
• Increased triglycerides
• Decreased HDL cholesterol
• Increased LDL cholesterol
Lactic acidosis/hyperlactatemia
Bone disease
• Osteonecrosis
• Osteoporosis
Wasting

Figure 1. **Fat accumulation: dorsocervical fat pad ("Buffalo hump")**

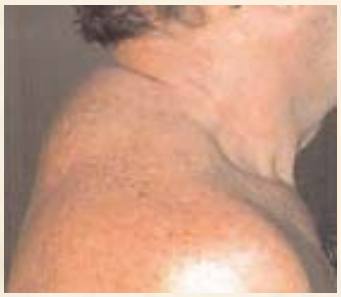


Figure 2. **Fat accumulation: abdominal (visceral) obesity**

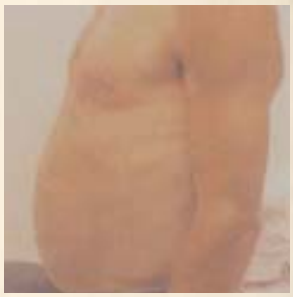


Figure 3. **Lipoatrophy: Facial fat loss with deepening of nasolabial fold**

Figure 4. **Lipoatrophy: Fat depletion of leg with prominence of veins and enhanced definition of musculature**

It is important to keep in mind that age is associated with a progressive trend toward increasing central body fat deposition and wasting of fat in the extremities.[9] Among participants in the Multicenter AIDS Cohort Study (MACS) and the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), the prevalence of increased abdominal fat was quite high even among HIV-negative participants.[10,11] However, peripheral fat wasting was rare in HIV-negative participants. The prevalence of peripheral fat wasting was 20% among HIV-positive men receiving combination ART for at least two years versus 1% to 2% among HIV-negative men.

Mechanism(s) of disease

Considerable controversy exists regarding the pathophysiologic mechanisms underlying the development of HIV-associated lipodystrophy. While the majority of researchers have advocated a view that this syndrome is predominantly a drug-related side effect mediated by contributions from both the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes of antiretroviral medications, some studies, such as the recent HIV Outpatient Study (HOPS), have demonstrated no evidence of antiretroviral class-specific effects.[12] Other investigators have suggested that HIV-associated lipodystrophy is an immune reconstitution or cytokine-mediated phenomenon.[13,14] Elevated levels of cytokines as well as macrophages capable of producing such cytokines have been reported in subcutaneous adipose tissue from lipoatrophic subjects.[15]

HIV-associated lipodystrophy has been viewed as a reciprocal syndrome in which peripheral fat loss is accompanied by central fat gain, including an increase in visceral adipose (intra-abdominal fat) tissue accumulation. However, the paradigm of increased central fat gain recently has been challenged by magnetic resonance imaging (MRI) findings within the FRAM analysis, which found that HIV-positive men who had the clinical syndrome of peripheral lipoatrophy had less adipose tissue in both peripheral and central depots than did HIV-positive men without peripheral lipoatrophy. Furthermore, HIV-positive men with or without the clinical syndrome of peripheral lipoatrophy had less adipose tissue in both peripheral and central depots compared with control subjects.[11]

Antiretroviral therapy

The HIV-associated lipodystrophy syndrome was first described in 1998, shortly after the introduction of PIs.[16] Thus, early studies focused on the role of PIs in the development of HIV-associated lipodystrophy, although PIs alone appeared to rarely cause lipodystrophy.[17] It is now clear that HIV lipodystrophy can develop in patients who have never been treated with PIs.[18,19] The use of NRTIs, stavudine (d4T) in particular, has been linked specifically to the development of the lipoatrophic component of HIV-associated lipodystrophy syndrome.[2,19,20]

In the Western Australian Cohort Study, the median time from initiation of PI-containing ART to clinically apparent peripheral lipoatrophy was 18.5 months

for patients receiving d4T-containing regimens compared with 26 months for patients receiving zidovudine (ZDV)-containing regimens.[20] However, combined PI and dual NRTI therapy leads to peripheral lipoatrophy dramatically faster than does dual NRTI therapy alone.[20] The risk of lipodystrophy increases with both duration of NRTI therapy and duration of PI therapy.[3,20,21] This finding is further supported by the FRAM analysis, in which the duration of treatment with d4T and the duration of treatment with the PI indinavir (IDV) were each associated with significant decreases in leg subcutaneous adipose tissue (SAT) but not visceral adipose tissue (VAT).[11] Nonnucleoside reverse transcriptase inhibitors (NNRTIs) have not been reported to result in lipodystrophic tendencies.[22]

Host factors

Although HIV-associated lipodystrophy is uncommon in the absence of ART, nondrug factors are also important. Older age has consistently been shown to be associated with increased lipodystrophy risk.[1-3,5,6] Race may be important, with higher rates of lipodystrophy seen in Caucasians.[3,6] Males appear more likely to develop peripheral lipoatrophy, whereas females have greater fat accumulation centrally. Viral load, CD4 count, prior AIDS diagnosis, immune reconstitution, and baseline body mass index (BMI) have been cited as important in some studies, but have not been linked consistently to HIV-associated lipodystrophy risk.[3,5,23]

Mitochondrial toxicity

There is now strong evidence that NRTI-induced mitochondrial toxicity plays a major role in the development of the lipoatrophic component of HIV-associated lipodystrophy syndrome. The NRTIs are known to have an inhibitory effect on mitochondrial DNA (mtDNA) polymerase gamma, the principal enzyme responsible for mtDNA replication. Because mtDNA encodes many of the oxidative-phosphorylation chain proteins, a decrease in mtDNA content theoretically could hinder aerobic respiration and other mitochondrial functions.[24] A decrease in mtDNA is indeed found in SAT from subjects with lipoatrophy.[25,26] However, more recent evidence suggests that the mitochondrial toxicity of NRTIs may involve not only the depletion of mtDNA but also negative effects on the proteins and enzymatic activity of the oxidative-phosphorylation system even prior to such depletion. Decreased transcription of mitochondrial RNA without significant depletion of mtDNA is seen by two weeks after initiation of dual-NRTI therapy (ZDV/lamivudine [3TC] or d4T/3TC) in HIV-negative controls, suggesting the NRTIs cause mitochondrial dysfunction by means other than through inhibition of DNA polymerase gamma.[27] Improvement in both mtDNA and complex I mitochondrial enzyme activity level as well as in the rate of adipocyte apoptosis have been demonstrated following removal of the offending NRTIs.[28] Protease inhibitors may compound the problem by inhibiting adipocyte differentiation and maturation.[29-31] The full molecular basis of this inhibition remains to be determined, but may entail inhibition of specific cellular proteases involved in maturation of nuclear lamin proteins and the adipogenic factor sterol regulatory element binding protein-1 (SREBP-1).[32]

In the general population, enlargement of the dorsocervical fat tissue ("buffalo hump") occurs in association with a state of glucocorticoid excess (Cushing syndrome). However, hypercortisolism has been excluded as a cause of buffalo hump in HIV-associated lipodystrophy, and the factors associated with the development of this form of fat accumulation remain unclear.[33]

Diagnosis

Diagnosis of HIV-associated lipodystrophy is typically made on clinical grounds, based on patient and physician assessment of body composition changes. Whereas case definitions for use as a research tool have been suggested, consensus is lacking and the applicability to clinical practice is unclear.[20,34] Diagnosis is hampered by several factors. Fat depletion in the periphery may be associated with the AIDS wasting syndrome, which typically is characterized by loss of both lean and fat tissue. Visceral fat accumulation may be associated with general weight gain that may occur shortly after initiating effective ART. In patients with stable weight, assessment of lipodystrophy relies on demonstration of changes in regional fat content following use of ART, and therefore, by necessity, requires knowledge of premorbid fat content and distribution.

Abdominal MRI and computed tomography (CT) are sensitive and specific measures of visceral fat, but they are costly and likely to remain primarily research tools.[35] In addition, CT scanning entails some radiation exposure. Single-slice CT measurements of the abdomen at the level of L4-L5 correlate strongly with whole-body measurements for both SAT and VAT.[36-38] Dual-energy X-ray absorptiometry (DEXA) adequately measures subcutaneous limb fat and may be utilized for studies of peripheral fat loss. However, DEXA is not appropriate for assessment of central adiposity, as it cannot distinguish between abdominal subcutaneous and visceral fat.[35] All anthropometric measurements suffer from wide inter- and intra-person variability among participants interpreting the tests, and require considerable training for the results to be reproducible.[35] Finally, bioelectrical impedance analysis (BIA) typically estimates whole-body composition. Whereas attempts have been made to assess regional-body composition using BIA, the methods remain unvalidated, and cannot be recommended at the present time.[39]

Although none of the above techniques has sufficient sensitivity, specificity, or cost-effectiveness value to be recommended for routine clinical use, it may be reasonable to document fat distribution prior to the initiation of ART by photographs and/or simple anthropometric means (weight, height, and circumferences of the arms, thighs, waist, and hips, and perhaps the neck).[1]

Therapy

Because their pathogenic mechanisms differ, fat accumulation and fat depletion are expected to require different therapeutic interventions. For peripheral lipoatrophy, switching antiretroviral drugs from NRTIs with high potential for mitochondrial toxicity to more "mitochondrially friendly" regimens has been demonstrated to result in some improvement in SAT. Otherwise, no effective treatment for HIV-associated lipodystrophy has been established. Evidence from the various approaches that have been studied is summarized in this section:

Switch therapies and NRTI-sparing regimens

PI withdrawal or substitution with an NNRTI is not helpful in correcting HIV-associated lipodystrophy, although dyslipidemia improves following these types of switches.[40-43] There is now substantial evidence that switching subjects off NRTIs known to have mitochondrial toxicity, in particular d4T, results in some increase in SAT. This improvement was observed following the substitution of either ZDV or abacavir (ABC) for d4T in the Trial to Assess the Regression of Hyperlactatemia and to Evaluate the Regression of Established Lipodystrophy in HIV-1-Positive Subjects (TARHEEL) study, which demonstrated mean increases by DEXA of 35% in arm fat, 12% in leg fat, and 18% in trunk fat at week 48 compared with baseline levels.[28] A switch from ZDV or d4T to ABC was demonstrated in the Mitochondrial Toxicity (MITOX) Extension Study to result in a mean gain in limb fat by DEXA of 1.26 ± 2.02 kg compared with 0.49 ± 1.38 kg in the ZDV/d4T control arm at week 104.[44] The time-weighted change for limb fat was significantly different between controls and those who switched antiretroviral agents (0.43 kg; $P = 0.008$). In other studies, a switch to a completely NRTI-sparing regimen of lopinavir/ritonavir (LPV/r) plus efavirenz (EFV) resulted in a median improvement after 104 weeks of 782 g of appendicular fat compared with a loss of 900 g in a group receiving EFV plus two NRTIs.[45] Similarly, a switch from a d4T- or ZDV-containing regimen to LPV/r plus nevirapine (NVP) resulted in a 17% median increase in subcutaneous thigh fat after 48 weeks.[46] Collectively, switching antiretroviral agents has resulted in statistically significant gains in peripheral fat; however, the clinical relevance of these improvements is unclear.

Switching antiretrovirals therefore may result in modest improvements, but care must be exercised to avoid virologic failure with such substitutions. In a randomized, open-label study of 236 patients, a higher rate of treatment discontinuation and a trend toward virologic failure occurred in the NRTI-sparing regimen arm (LPV/r plus EFV) compared with EFV plus two NRTIs.[47] The return of peripheral fat in all studies, however, has been partial and does not restore the level present before starting ART, leading to concerns that fat loss may be partially irreversible or that a prolonged recovery phase is needed for complete resolution of lipoatrophy.

Anabolic steroids

Pharmacologic interventions have yielded mixed results. Decreased testosterone levels are seen in HIV-positive men and are associated with visceral obesity in the general population.[48] Although testosterone replacement has been associated with decreases in VAT and improvements in insulin sensitivity in HIV-negative men, testosterone replacement did not reduce VAT over a 24-week period in HIV-positive patients with mildly to moderately low testosterone levels.[49,50] Testosterone replacement was associated, however, with a net loss of limb SAT and total adipose tissue content. It is not known whether these changes correlate with laboratory assessments of insulin, glucose, or lipid metabolism.

Growth hormone

In a prospective, open-label trial of 30 HIV-positive patients, supraphysiologic doses of recombinant human growth hormone (6 mg/day) administered over the course of 24 weeks led to a significant decrease in VAT. Unfortunately, side effects including hyperglycemia, arthralgias, and fluid retention were common, and body composition changes reverted to pretreatment status after the therapy was stopped.[51] Lower, pharmacologic doses of growth hormone have demonstrated consistent declines in VAT, but alterations in glucose homeostasis continued to occur.[51,52]

Metformin

Metformin was evaluated at a dose of 500 mg twice a day in a randomized controlled trial of 26 HIV-positive subjects.[53] A trend toward a decrease in VAT as measured by CT was seen but was not statistically significant. This decrease in VAT was associated with general weight loss and proportional reduction in SAT. Diastolic blood pressure and insulin resistance were noted to improve significantly in the treatment arm. No increase in lactate or liver transaminase levels was observed, and mild diarrhea was the most commonly noted adverse effect of metformin.

Thiazolidinediones

Another class of insulin-sensitizing agents, the thiazolidinediones, can increase adipogenesis *in vitro*, suggesting that these agents may be able to reverse subcutaneous fat loss. Thiazolidinediones are peroxisome proliferator-activator receptor (PPAR)-gamma agonists. Adipose tissue from HIV-positive patients has reduced expression of SREBP-1c and PPAR-gamma.[32] Troglitazone increased SAT and reduced VAT in HIV-negative patients with type 2 diabetes mellitus and in those with various syndromes of genetic and acquired lipodystrophy.[54-56] However, this drug was withdrawn from the market in 2000 because of severe liver toxicity.[57] The limited number of studies available to date involving HIV-positive patients have not shown consistent improvements in VAT or in subcutaneous lipoatrophy with thiazolidinedione treatment.[58-60] Rosiglitazone at 4 mg twice daily failed to improve subcutaneous limb fat compared with placebo after 48 weeks of treatment in 108 lipoatrophic HIV-positive patients.[61] As a result, the authors state that rosiglitazone cannot be recommended for the treatment of lipoatrophy in HIV-positive adults.

Uridine

Uridine is a pyrimidine nucleoside that has been shown to prevent the adverse effects of zalcitabine (ddC) on mitochondrial function in HepG2 cells with respect to lactate synthesis, hepatocyte proliferation, intracellular lipids, and cyclooxygenase-2 levels.[62] Similarly, in 3T3-F442A preadipocytes, uridine prevented toxicity-related effects of pyrimidine analogs on adipocytes, including apoptosis, intracellular lipids, mitochondrial mass, membrane potential, and mtDNA depletion.[63] Moreover, uridine does not appear to interfere with the efficacy of ART.[64]

In a small pharmacokinetic study, uridine levels increased after supplementation, peaked after 1.3 hours, then returned to baseline after 24 hours.[65] Adequately powered safety and efficacy studies are needed to determine the clinical effects of uridine in patients with lipoatrophy.

Dietary and nonpharmacologic measures

There are limited data to support a role for specialized dietary supplements in HIV-positive patients with lipoatrophy.

However, recent data suggest there may be some benefit in treating or preventing NRTI-mediated mitochondrial dysfunction with dietary supplementation.

Exercise

Hypocaloric diets are recommended for overweight patients with BMI >27, although rapid weight loss should be avoided. Exercise, both aerobic and resistance training, can be beneficial for cardiopulmonary fitness and strength without adverse effect on virologic or immunologic control.[66-68] Although both diet and exercise can reduce central adiposity while improving glycemic control and lipid profiles, they also may lead to loss of peripheral subcutaneous fat.[69]

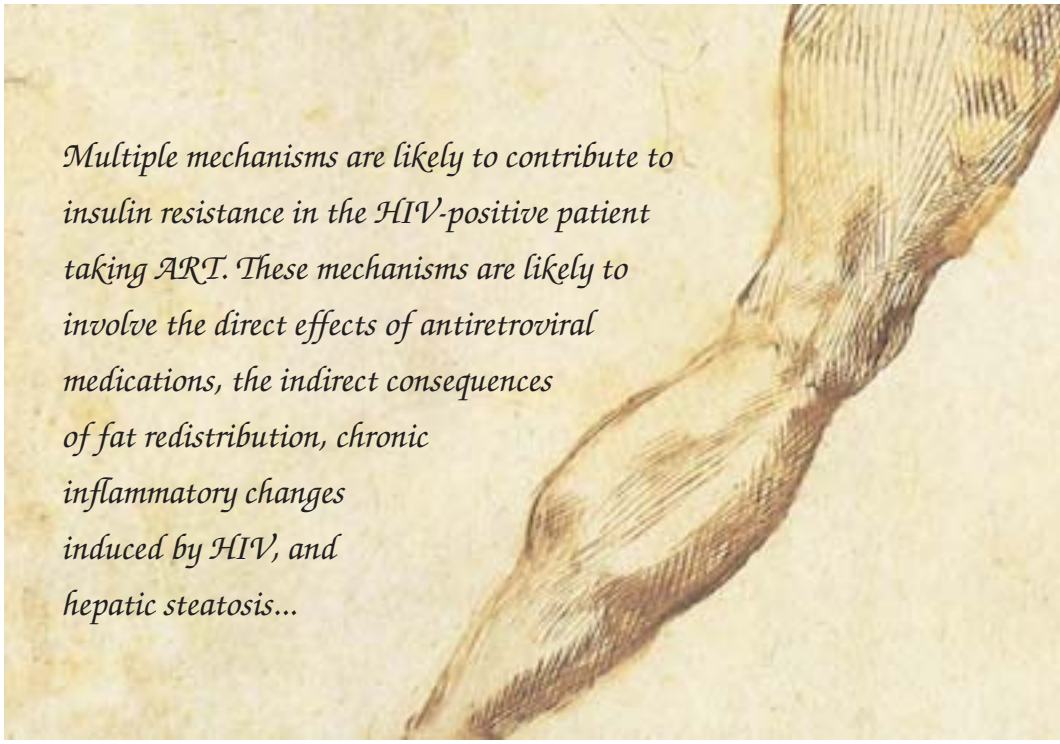
Plastic surgery

Facial lipoatrophy is a particularly distressing aspect of lipodystrophy. Plastic surgery has gained increasing attention in the HIV-positive community due to the limited efficacy of other therapeutic options. Because transplantation of the patient's own fat tends to result in absorption and disappearance of fat cells in a matter of weeks, much interest has focused on synthetic, nonbiodegradable implants, for which long-term safety and efficacy data are lacking. Poly-L-lactic acid, a biodegradable synthetic polymer, is the only product currently approved by the US Food and Drug Administration (FDA) for the treatment of facial lipoatrophy. The disfigurement resulting from facial lipoatrophy and the potential for extreme psychological distress create an urgent need for research into other modalities of palliative therapy.

Insulin Resistance

Background and definition

Insulin resistance and glucose intolerance were reported to be uncommon in HIV-1 infection prior to the use of potent antiretroviral regimens. The era of combination ART has seen an increase in these abnormalities. Fasting glucose levels from a group of 1,278 men in the MACS cohort showed that 14% of HIV-positive men on ART had diabetes mellitus compared with 5% of HIV-negative men adjusted for age and BMI. Moreover, the incidence of diabetes mellitus over a four-year observation period in HIV-positive men with ART exposure was 4.7 cases per 100 person-years, a level more than four times that of HIV-negative control men.[70] The well-known long-term cardiovascular consequences of insulin resistance and diabetes have raised concerns regarding such risks in the HIV-positive population currently being treated with ART.[71,72] Disorders of glucose metabolism are defined in Table 2.



Mechanism(s) of disease

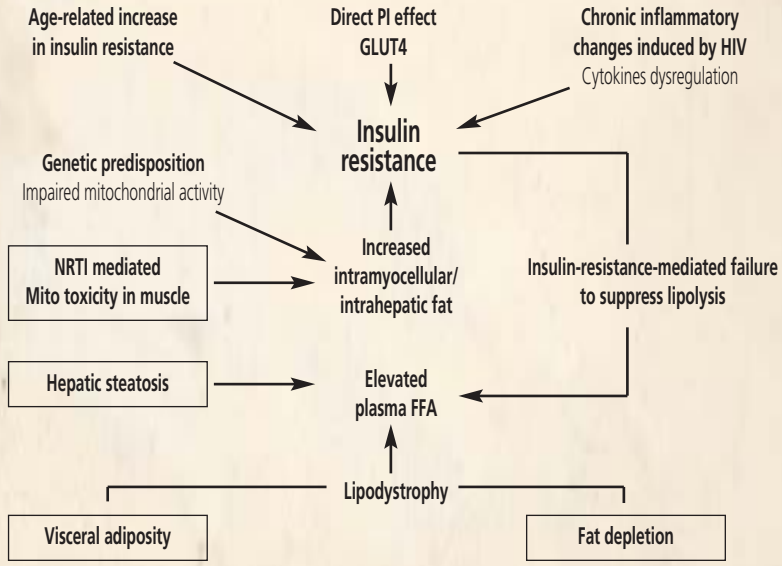
Impairment of glucose metabolism is thought to result predominantly from tissue insensitivity to the effect of insulin (insulin resistance). A compensatory increase in insulin secretion is needed to inhibit hepatic gluconeogenesis and to increase muscle uptake of glucose.

Multiple mechanisms are likely to contribute to insulin resistance in the HIV-positive patient taking ART. These mechanisms are likely to involve the direct effects of antiretroviral medications, the indirect consequences of fat redistribution, chronic inflammatory changes induced by HIV, and hepatic steatosis, as summarized in Figure 5.[73] The PI IDV directly induces the development of insulin resistance when given as a short course or as a single dose in HIV-negative patients.[74,75] This direct response is likely mediated by impaired cellular glucose uptake due to inhibition of both the Glut4 glucose transporter and glucose phosphorylation.[76,77] Reduced insulin sensitivity may also be a result of lipodystrophy mediated by the elevated blood levels of free fatty acids (FFA) induced by both the fat accumulation and depletion components of lipodystrophy. Elevation of FFA may interfere with cellular glucose transport through a reduction in the phosphorylation of insulin receptor substrate-1-associated phosphatidylinositol 3-kinase, which results in impaired intracellular signaling and insulin resistance, especially in muscle and hepatic tissue.[78-80] Interestingly, increases in lipolysis and elevated blood levels of FFA have been found to be independently associated with both accumulation of VAT (a more metabolically active form of fat) and depletion of peripheral SAT.[81,82] Finally, it is now recognized that a variety of proteins derived from adipocytes and adipose stromal cells act both locally and distally to regulate fat cell differentiation and to sense and adjust systemic energy balance. HIV infection and antiretroviral-mediated disturbances in the quantity and distribution of fat may disrupt the normal cytokine regulation of glucose homeostasis. Of particular interest is an adipokine called adiponectin (ACRP-30, adipoQ) that may have insulin-sensitizing properties.

Table 2. **Disorders of glycemic homeostasis**

	Definitions
Insulin resistance	A condition characterized by decreased tissue sensitivity to the action of insulin
Impaired glucose tolerance	Elevated blood glucose of 140-199 mg/dL on oral glucose tolerance testing (blood glucose measured 2 hours after a 75-gram oral glucose load)
Impaired fasting glucose	Fasting blood glucose of 110-125 mg/dL
Diabetes mellitus	Fasting blood glucose ≥126 mg/dL, or blood glucose level ≥200 mg/dL on an oral glucose tolerance test

Figure 5. **Etiologies for the development of HIV-1 related insulin resistance**



Source: Shikuma CM, Day LJ, Gerschenson M. Insulin resistance in the HIV-infected population: The potential role of mitochondrial dysfunction. *Curr Drug Targets Infect Disord.* 2005;5(3):255-62. Reproduced with permission.

A correlation between low adiponectin levels and decreased peripheral subcutaneous fat has been reported.[83]

The effect on insulin resistance of initial exposure to ART by quantitative insulin-sensitivity check index (QUICKI) was assessed within the MACS cohort.[84] Comparing HIV-negative men with HIV-positive men stratified by therapy status for the preceding six months (no ART, mono or dual NRTI, ART including a PI, or ART without a PI), insulin resistance was higher in all HIV-positive subjects compared with HIV-negative controls, suggesting a potential role for HIV per se as well as for antiretroviral medications.[85] After adjusting for age, BMI, ethnicity, nadir CD4 count, hepatitis C (HCV) serostatus, and family history of diabetes mellitus, subjects treated with ART including a PI had the highest insulin resistance compared with the other groups. Total cumulative exposure (years of use for each therapy class) to NRTIs, but not to PIs or NNRTIs, was associated with the development of insulin resistance, suggesting an indirect lipoatrophic effect of NRTIs on insulin resistance rather than a direct effect.[85] Of individual medications examined, d4T was associated with the highest risk of hyperinsulinemia.

Diagnosis

The International AIDS Society-USA Panel recommendations on the management of metabolic complications advise that fasting glucose should be assessed before and during treatment (prior to starting ART, three to six months after starting, and annually thereafter) with a regimen containing one or more PI.[1] It may be appropriate to extend this recommendation to all subjects initiating antiretroviral regimens, given that insulin resistance may also be seen with regimens that do not include a PI, particularly in association with the development of lipodystrophy. Serial fasting plasma glucose assessments and/or oral glucose tolerance testing may help to identify patients with impaired glucose tolerance, and may be especially helpful in those at risk for type 2 diabetes mellitus.

Therapy

In ART-naive patients with preexisting impaired glucose tolerance, consideration should be given to avoiding the use of older-generation PIs, such as IDV, in initial therapy. Among PIs, atazanavir (ATV) and amprenavir/fosamprenavir (APV/FPV) may be less likely to cause impaired glucose tolerance.[86,87] In those patients already taking older PIs who develop diabetes, switching antiretroviral regimens to improve insulin sensitivity may be considered with attention to possible side effects of the new regimen and risk of virologic failure. Short-term improvement in insulin resistance has been demonstrated with the substitution of an NNRTI or ABC for the PI component of an antiretroviral regimen.[42,88,89] The choice of the NRTI backbone is also important in glucose homeostasis, as d4T use is associated with the highest risk of hyperinsulinemia. The initial use of ABC or tenofovir (TDF) may reduce overall insulin resistance.

Lifestyle modification promoting healthy diet and exercise is important. The Diabetic Primary Prevention Trial found that weight loss, healthy diet, and exercise delayed the onset of diabetes in patients with impaired glucose tolerance.[90] For patients with persistent fasting hyperglycemia requiring drug therapy, insulin-sensitizing agents (such as metformin) and thiazolidinediones (such as rosiglitazone and pioglitazone) have been shown to be safe and effective in reducing insulin resistance in the HIV-positive population. Metformin has been shown to improve visceral fat accumulation, fasting lipid profile, and endothelial function.[91] The combination of exercise training with metformin significantly improves cardiovascular and biochemical parameters more than metformin alone in HIV-positive patients with fat redistribution and hyperinsulinemia.[92] Close monitoring for the development of lactic acidemia is warranted with metformin use. Rosiglitazone therapy is associated with improvement in insulin sensitivity.[60,91] Because of the known association of the thiazolidinediones with liver dysfunction, serial monitoring of liver enzymes is warranted. Oral sulfonylureas,

meglitinides, and insulin should be reserved for severe cases of diabetes in which insulin-sensitizing agents are ineffective or contraindicated. Testosterone therapy has been found to improve insulin sensitivity in hypogonadal men, but should be considered only in this specific subgroup of HIV-positive men because of the potential adverse effects of excess testosterone.[48]

Dyslipidemia

Background and definition

Abnormalities of lipid metabolism are common complications of HIV disease and ART. Similar to the link suggested between atherosclerosis and chronic infections such as *Chlamydia pneumoniae*, the inflammatory response to chronic HIV infection, which is probably mediated by cytokines, may in itself be proatherogenic.[93] Prior to the availability of effective ART, proatherogenic lipid profiles characterized by reduced levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, but with appearance of small dense LDL (subclass pattern B) and increased triglyceride levels were reported.[94,95] Small dense LDL is believed to be proatherogenic because it is particularly susceptible to oxidation and can penetrate the endothelium and bind to intima proteoglycans more effectively than large buoyant LDL, resulting in retention in the arterial wall. Since the initiation of potent ART, particularly with the use of PIs, elevations in triglycerides and LDL and total cholesterol are commonly seen in practice. In a prospective study of 221 HIV-positive patients followed for a median of five years, the incidence of new-onset hypercholesterolemia and hypertriglyceridemia was 24% and 19%, respectively.[96]

These proatherogenic lipid profiles have raised concerns about increased cardiovascular disease risk in the HIV-positive population. Metabolic syndrome is common among HIV-positive men, with a prevalence of 13% to 23%.[97] Lower CD4 counts, tobacco use, advancing age, and combination ART use were associated with greater risk for metabolic syndrome within the Strategies for Management of Anti-Retroviral Therapy (SMART) trial.[98] This trial compared episodic use of ART based on CD4 count against continuous therapy, and was stopped early after an excess of AIDS-defining events as well as an increase in major complications including cardiovascular events in the group receiving episodic ART. These findings suggest a combined effect of HIV infection and ART on overall cardiovascular disease risk.

Although the exact incidence of cardiovascular disease among HIV-positive patients treated with ART is a matter of debate, results from prospective studies suggest increased risk. The HOPS, a prospective observational cohort study, reported an increased incidence of myocardial infarction and angina in HIV-positive patients taking PIs compared with those not taking PIs. This increased risk remained evident even after adjustment for other risk factors, including smoking, gender, age, diabetes, hyperlipidemia, and hypertension.[99] However, the investigators noted that most of the patients who had a myocardial infarction or an anginal episode also had traditional risk factors for cardiovascular disease besides hyperlipidemia, such as smoking, hypertension, and insulin resistance. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study), a prospective assessment of 23,490 patients from 11 cohorts on three continents, found that combination ART was associated with a 27% relative increase in the rate of myocardial infarction per year of exposure during the first seven years of treatment.[100]

Mechanism(s) of disease

Protease inhibitors have been implicated as a major cause of the lipid abnormalities seen with ART. Use of PIs is associated with the development of dyslipidemia independent of treatment with other drugs, viral load, or body weight changes. Different PIs have various effects on lipid metabolism. Ritonavir (RTV) has the greatest effect on levels of triglycerides, LDL, and cholesterol, whereas IDV has minimal effect.[75,101] Interestingly, ATV has been shown to have a beneficial effect on serum triglycerides, LDL, HDL, and total cholesterol levels.[102,103] Protease inhibitors are thought to inhibit the degradation of apolipoprotein B, which in turn results in lipid elevations.[104] Genetic susceptibility has been found to play an important role in lipid metabolism in patients receiving PIs. Patients who are heterozygous or homozygous for the apolipoprotein E-2 genotype have been found to have higher serum triglyceride and cholesterol levels when receiving PIs.[105,106]

The effect of NRTIs on dyslipidemia is difficult to assess due to the usual coadministration with NNRTIs or PIs. However, as a class, NRTIs appear to have less of a tendency than PIs to cause dyslipidemia, particularly on a short-term basis. The combination of ZDV/3TC/ABC given as a first-time antiretroviral regimen to antiretroviral-naive subjects caused little to no changes in triglyceride and cholesterol levels over the first 24-week period of administration.[107] However, d4T has been demonstrated to cause dyslipidemia. A prospective, multicenter study by the RECOVER Study Group found that HIV-positive patients who replaced d4T with TDF had significant decreases in triglyceride and cholesterol levels. This suggests, at least partly, a d4T-associated dyslipidemia.[108] Additionally, lipoatrophy epidemiologically linked to the use of NRTIs has been associated with increases in free fatty acid production and triglyceride levels.[19] Medications within the NNRTI class also have effects on lipid levels, although not to the same degree as PIs. The use of EFV in addition to an NRTI backbone of ZDV/3TC with or without ABC has been demonstrated to result in increased total cholesterol and directly measured LDL as well as HDL cholesterol levels.[107] Compared with PIs, use of NNRTIs has been noted to result in generally higher HDL cholesterol levels.[109,110] Favorable decreases in levels of cholesterol, triglycerides, or both generally have been demonstrated following a switch from PIs to NVP or EFV.[41,42,88,111]

Diagnosis

Prospective serial evaluation for dyslipidemia in patients with HIV appears warranted considering the association between dyslipidemia and increased cardiovascular risk. In addition, triglyceride levels >1,000 mg/dL (11.3 mmol/L) are associated with an increased risk of pancreatitis. As suggested in preliminary guidelines by the Adult AIDS Clinical Trials Group (ACTG) Cardiovascular Disease Focus Group, it is reasonable to obtain a fasting lipid profile at baseline and approximately three months after starting a new ART regimen.[112] If the lipid profile is normal, annual repeats are recommended.

Because optimal management of dyslipidemia in HIV-positive subjects is not established fully, it appears reasonable to follow the general guidelines of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) as a reference and framework for identifying patients who require lipid-lowering interventions.[113] The NCEP has a risk assessment tool for estimating the 10-year cardiovascular disease risk of an individual. A 10-year cardiovascular disease risk >10% indicates a need for intervention.

Lipid panels should be performed in a fasting state (no food or drink except water for at least 12 hours) and should include triglyceride, HDL, LDL, and total cholesterol levels. The Friedewald equation can be used to calculate LDL cholesterol (in mg/dL): calculated LDL cholesterol = total cholesterol - HDL cholesterol - triglycerides/5.[114] The Friedewald equation is not accurate for triglyceride levels >400 mg/dL, and a direct LDL cholesterol measurement should be obtained. If direct LDL cholesterol measurement is not possible, non-HDL cholesterol levels (total cholesterol minus HDL cholesterol) at least 30 mg/dL greater than the established upper limit of LDL cholesterol indicate that intervention is appropriate.[1]

In addition to lipid levels, evaluations for comorbidities such as hypogonadism, thyroid disease, liver disease, and alcoholism are important initial steps in the evaluation of dyslipidemia in HIV-positive patients. Recognition of the metabolic syndrome is also an important step in cardiovascular risk stratification. Identification of the metabolic syndrome, as defined by the NCEP ATP III, is shown in Table 3.[113]

Table 3. **National Cholesterol Education Program's Adult Treatment Panel III Report on the Clinical Identification of the Metabolic Syndrome**

The metabolic syndrome can be identified as the presence of three or more of these components:

Risk factor	*Defining level*
Abdominal obesity, given as waist circumference*	
Men	>102 cm (> 40 in)
Women	>88 cm (>35 in)
Triglycerides	150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	<50 mg/dL
Blood pressure	130/85 mm Hg
Fasting glucose	110 mg/dL

*Being overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is correlated more highly with the metabolic risk factors than is an elevated body mass index. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

Some male patients can develop multiple metabolic risk factors when the waist circumference is increased only marginally, eg, 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference.

The American Diabetes Association has established a cutpoint of 100 mg/dL, above which persons have either prediabetes (impaired fasting glucose) or diabetes. This new cutpoint may be used to define an elevated glucose as one criterion for the metabolic syndrome.

Therapy

Randomized clinical trials to establish optimal treatment of ART-associated hyperlipidemia have not been completed. According to general NCEP ATP III guidelines, lifestyle modification is essential; smoking cessation, dietary modification (American Heart Association step 1 and 2 diets), and regular exercise should be promoted. Only after lifestyle modification has proved ineffective or when lipid levels are elevated severely are lipid-lowering agents necessary. For elevated LDL cholesterol, HMG-CoA reductase inhibitors (statins) have produced favorable responses.[115] Use of these drugs must be undertaken with caution, as elevated levels of statins resulting from the inhibitory effect of PIs on cytochrome P450 may result in myositis and rhabdomyolysis. The preferred statins are pravastatin or atorvastatin, as these agents have relatively modest pharmacokinetic interactions with antiretrovirals.[116,117] A lower initial starting dosage of atorvastatin (10 mg daily) is recommended. Efavirenz has been shown to reduce the inhibition of HMG-CoA reductase activity and therefore may result in diminished antilipid efficacy of statins.[118] Higher doses of statins to control dyslipidemia may be necessary when coadministered with EFV. Results from ACTG study A5087 found monotherapy with either pravastatin or fenofibrate for HIV-related dyslipidemia safe but unlikely to achieve the composite NCEP goal. Pravastatin appears to be effective primarily in lowering LDL, while subjects who received fenofibrate had larger increases in HDL and decreases in triglycerides. Dual therapy appeared safe, although the relative risk of rhabdomyolysis may be increased with combination therapy. Manufacturers currently do not recommend routine creatine kinase (CK) surveillance to detect myositis when statins are used in the general population. The utility of such surveillance in the HIV-positive population is unclear as isolated elevations of CK of uncertain clinical significance are seen frequently in HIV-positive patients. It seems prudent, however, to inform the patient of this potential side effect and to maintain a high index of suspicion for myalgias and other signs and symptoms of myositis and rhabdomyolysis. It may be best to avoid bile acid sequestrants, as these may interfere with absorption of antiretroviral drugs. The use of ezetimibe in combination with statin therapy is being studied.[119,120]

For hypertriglyceridemia (serum triglyceride levels >500 mg/dL), fibric acid analogs such as gemfibrozil and fenofibrate have been used. The magnitude of reduction of LDL, total cholesterol, and triglycerides through the use of statins, fenofibrate, or the combination of the two has been less than robust in patients taking PIs.[121-123] The International AIDS Society-USA Panel recommends that, when combination therapy with a fibric acid derivative and a statin is anticipated in the setting of hypertriglyceridemia accompanied by LDL cholesterol elevation, therapy should begin with a statin, followed by addition of the fibric acid derivative after month four if the response is suboptimal. Although niacin may worsen insulin resistance, the use of niacin may

be safe for the treatment of hypertriglyceridemia in patients at low risk for glucose intolerance. The safety and efficacy of niacin in combination with ART has been investigated in a small number of studies.[124-126] Fish oil has been shown in a randomized study to reduce triglyceride levels by 26% compared with placebo.[127] When fish oil was combined with fenofibrate, further triglyceride lowering was observed.[128]

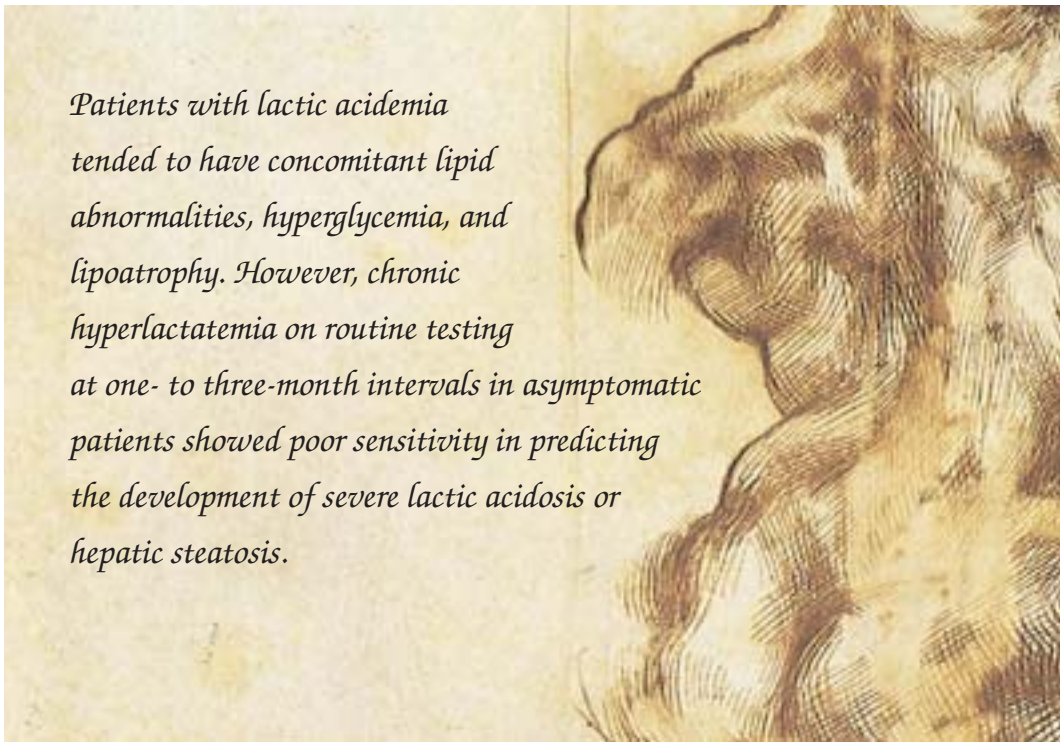
Hyperlactatemia and Lactic Acidosis

Background and definition

Lactic acidemia has been associated with NRTI use since the early 1990s. Lactic acidemia refers to increased plasma lactate (hyperlactatemia) that does not cause an abnormal blood pH, whereas lactic acidosis consists of a high lactate level accompanied by metabolic acidosis and decreased blood pH. The spectrum of disease within this syndrome ranges from fulminant decompensated multiorgan dysfunction characterized by severe acidosis and hemodynamic instability, to less-severe symptomatic hyperlactatemia with hepatic steatosis (fatty liver), to intermittent or chronic low-grade hyperlactatemia without acidosis, steatosis, or symptoms.

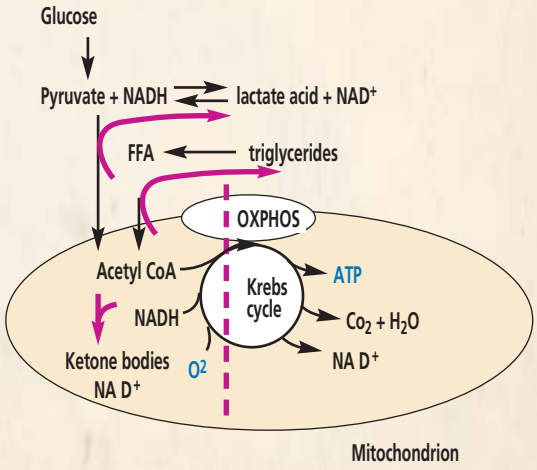
Although most cases of lactic acidemia are asymptomatic, a variety of nonspecific presenting complaints have been described. The most common symptoms include nausea, vomiting, and diffuse abdominal pain. Fatigue, weakness, weight loss, tachypnea or dyspnea on exertion, arrhythmias, and neurologic findings have also been reported in the absence of gastrointestinal complaints.[1,129] Liver abnormalities, including hepatomegaly, hepatic steatosis, and elevated serum transaminases are common in symptomatic hyperlactatemia and almost ubiquitous in NRTI-induced lactic acidosis.[1,129-134] Onset of symptoms is usually subacute, occurring over weeks to months, although acute fulminant cases associated with multiorgan (especially liver) dysfunction occur rarely.[129]

Several large observational studies have been performed to determine the prevalence of and risk factors for lactic acidemia.[134-137] Published estimates of the prevalence of lactic acidemia range from 8% to as high as 29% of patients receiving at least one NRTI,[1,137] though failure to follow stringent guidelines for lactate collection may have led to overestimation in earlier studies.[138] Mild asymptomatic acidemia does not appear to predict progression to more severe acidemia or symptomatic disease (symptomatic acidemia or lactic acidosis syndrome); chronic mild asymptomatic hyperlactatemia with stable lactate concentrations of 1.5 mmol/L to 3.5 mmol/L was the most common pattern of hyperlactatemia observed among 349 participants in the Western Australian Cohort Study.[130] The Swiss Cohort Study of 880 patients on ART receiving treatment in one of seven centers in Switzerland found increased risk of lactic acidemia with d4T use compared with ZDV-containing regimens, with an incidence of 11% versus 4.2%, respectively.[134] Didanosine (ddI) also conferred increased risk, whereas ZDV and 3TC were associated with comparatively lower risk of lactic acidemia. Patients with lactic acidemia tended to have concomitant lipid abnormalities, hyperglycemia, and lipoatrophy. However, chronic hyperlactatemia on routine testing at one- to three-month intervals in asymptomatic patients showed poor sensitivity in predicting the development of severe lactic acidosis or hepatic steatosis.[130] Many of these findings were demonstrated in the Aquitaine Cohort of 768 HIV-positive participants; increasing age and CD4 count <500 cells/µL also were associated with the development of lactate elevations in this group.[137] Children with *in utero* or postnatal exposure to nucleoside analogs also appear to be at risk for hyperlactatemia. In one study, nearly half of 127 infants with NRTI exposure had at least one elevated lactate measurement over the course of one year. Fortunately, most of these elevations were asymptomatic and self-limited; this finding has been confirmed in other series.[139,140] So far, studies have not demonstrated any association between NNRTI or PI therapy and lactic acidemia.



It has been estimated that symptomatic hyperlactatemia occurs at a rate of 13.6 to 14.5 per 1,000 patient-years, and that lactic acidosis occurs less frequently, at a rate of 1.2 to 3.9 events per 1,000 patient-years in HIV-positive patients receiving NRTIs.[141] The high mortality (33% to 57%) of NRTI-associated lactic acidosis has prompted investigation of specific predictors of acidosis. The largest case series of 12 Spanish patients with literature review of 60 additional cases of ART-associated lactic acidosis found presenting

Figure 6. **Increased lactic acid production**



NRTI-mediated mitochondrial dysfunction leads to a decrease in oxidative phosphorylation resulting, among other effects, in increased anaerobic metabolism of glucose, characterized by conversion of pyruvate into lactic acid. (Reproduced with permission.)

Table 4. **Adult AIDS Clinical Trials Group guidelines for venous lactate specimen collection**

1. Have subject sit relaxed for five minutes prior to venipuncture.
2. Instruct subject not to clench the fist before or during the procedure and to relax the hand as much as possible.
3. If possible, do not use a tourniquet. If a tourniquet is necessary, apply tourniquet lightly and draw lactate before collecting the other samples, with the tourniquet still in place.
4. Collect the blood in a chilled gray-top (sodium fluoride/potassium oxalate) tube.
5. Place the specimen immediately on ice and send to laboratory for immediate processing, preferably within 30 minutes of collection.
6. If random lactate is elevated, repeat as above, with the following additional patient instructions: no alcohol within 24 hours, no exercise within 8 hours, and no food or drink except water within 4 hours of the draw.

complaints mirroring those of less-severe acidemia. Viral load, CD4 count, use of specific NRTIs, and age were not predictive of increased disease severity. Stavudine was the thymidine analog used in 48% of cases, whereas ZDV was used in 45%, with a median nine months of therapy prior to presentation. Women were overrepresented, accounting for 43% of severe acidosis cases, though women account for approximately 20% of HIV-positive patients in the developed world. On multivariate analysis, only lactate level >10 mg/dL was associated with increased mortality (odds ratio [OR]: 13.23).[129] Pregnancy also may be a risk factor for more severe disease, and cases of acidosis with maternal and fetal deaths have been reported.[142,143] Patients with preexisting liver disease and hepatitis B virus (HBV) and HCV coinfection are overrepresented in both lactic acidemia and lactic acidosis.[144] Concomitant use of ddI and ribavirin in HIV/HCV-coinfected patients may represent a risk factor for lactic acidosis as well as for other syndromes attributed to NRTI-mediated mitochondrial toxicity.[145] A case of lactic acidosis in association with coadministration of TDF and ddI has also been reported, possibly related to augmented ddI levels with this antiviral combination.[146] Finally, a case-control study involving nine patients with lactic acidosis found creatinine clearance <70 mL/min and low nadir CD4 count to be most strongly associated with lactic acidosis risk.[147]

Mechanism(s) of disease

At a cellular level, lactate is the metabolic product of glycolysis under anaerobic conditions or when mitochondrial oxidative function is impaired. Lactic acidosis is believed to result from the overproduction of lactate as a consequence of NRTI-induced mitochondrial toxicity. The proposed mechanism of this drug toxicity is the inhibition of mtDNA polymerase gamma, the enzyme responsible for replication of mtDNA. Diminished polymerase activity decreases the amount of mtDNA and its gene products, which include proteins involved in oxidative phosphorylation, resulting in impaired aerobic metabolism and hyperlactatemia.[1,129] Didanosine and d4T show relatively high inhibition of DNA polymerase gamma *in vitro*, consistent with the finding of increased risk of lactic acidemia with these NRTIs (see Figure 6).[129]

Venous or arterial lactate reflects the net balance between lactate production and release from metabolically active tissues and lactate uptake by tissues (predominantly liver and kidney) with the capacity to oxidize lactate or use it as a substrate for gluconeogenesis. Homeostatic regulation is highly efficient, with conditions of lactate excess normally leading to augmentation of lactate clearance by the liver, kidneys, lungs, and muscle. Sustained elevations in blood lactate levels therefore indicate a significant loss of homeostasis.[130,148] Possible explanations for the lactic acidosis/acidemia syndrome include massive overproduction of lactate, marked decrease in the ability to oxidize lactate, or, most likely, a combination of both. The almost-uniform involvement of liver pathology in severe cases of lactic acidosis and acidemia suggests that hepatic dysfunction with respect to lactate metabolism may be an important component of this syndrome.

Diagnosis

Measurement of blood lactate is indicated in patients on NRTI therapy who present with the signs and symptoms described above, and in those with low bicarbonate, chloride, or albumin levels; elevated anion gap; unexpected increases in liver enzymes; or new onset of clinical liver failure. Anion gap has not been found to correlate reliably with lactic acid level and a normal anion gap cannot be used to exclude the diagnosis of hyperlactatemia or acidosis. Routine measurements of venous lactate are not indicated in asymptomatic patients because of the poor positive predictive value for future symptomatic lactic acidosis or hepatic steatosis.[130,149]

Care must be taken to ensure proper collection of lactate samples, as failure to do so may lead to falsely elevated lactate levels. Guidelines such as those developed by the Adult ACTG may be helpful in this regard (Table 4). If carefully collected,

venous lactate is equivalent to the arterial level in most clinical situations.[150] It is particularly important to arrest continued anaerobic metabolism by blood cellular components following a blood draw by the use of sodium fluoride/potassium oxalate tubes.[151] However, these guidelines are based on scant data, and the exact importance of hydration, avoiding prior exercise, the need to collect blood without fist clenching or tourniquet application, and the need for ice or refrigeration is unknown. In one multicenter study, frozen storage of lactate specimens from HIV-positive subjects was associated with only small increases (0.4 to 0.6 mmol/L) in lactate measurements at 64 weeks compared with baseline values.[152]

The significance of a single lactate value is difficult to interpret, and values over time show wide variations in a single patient. It is important, therefore, that any elevated value be confirmed with repeat testing with careful attention to specimen collection guidelines.

Therapy

The management of hyperlactatemia depends on the degree of elevation and the severity of symptoms.

Lactic acidosis

Considering the high morbidity and mortality of lactic acidosis and the potential for acute presentation, a high index of suspicion is essential for the successful management of this syndrome. In published reports of HIV-related lactic acidemia, overall mortality was 80% in patients with lactate levels >90 mg/dL (10 mmol/L), but no patient with lactate levels <90 mg/dL died.[1] Over time, characteristic features that may assist in identification of subjects with NRTI-induced lactic acidosis have emerged: patients almost always have hepatic steatosis and are symptomatic with nausea, vomiting, anorexia, abdominal pain or distension, tender hepatomegaly, fatigue, malaise, and prostration.[144]

Withdrawal of the inciting NRTI drug forms the cornerstone of therapy for this group of participants. Other antivirals should also be held in the acute setting to limit the development of viral resistance until appropriate ART can be reinstituted safely. In addition, therapy directed at the correction of acidosis is indicated and may include hemodynamic or respiratory support in an intensive care unit as well as the use of hemodialysis in severe cases.[144] Additional therapies without proven efficacy that have been used empirically in subjects acutely ill with this syndrome include intravenous thiamine,[153,154] riboflavin,[149] L-carnitine,[155,156] coenzyme Q,[155,157] and vitamin C.[155]

Symptomatic hyperlactatemia

Management depends on the severity of symptoms and the judgment of the physician regarding the clinical significance of the lactate elevation. There are no randomized, controlled clinical trials in HIV-positive patients to evaluate how and when withdrawal of antiretrovirals should be considered in those patients with hyperlactatemia without acidosis. However, the International AIDS Society-USA Panel recommends withdrawal of antiretrovirals in all patients with lactate levels >90 mg/dL (10 mmol/L) and in all *symptomatic* subjects with lactate levels >45 mg/dL (5 mmol/L).[1] It may be reasonable to consider NRTI withdrawal in symptomatic subjects with any degree of lactate elevation if no other reasons for symptoms are identified.

Aside from discontinuation of ART, the treatment of severe hyperlactatemia is supportive. In addition, as with lactic acidosis, there are case reports of cofactor administration using thiamine, riboflavin, L-carnitine, coenzyme Q, and antioxidants. These agents may be beneficial, although randomized trials of their efficacy are lacking. Reinstitution of ART with alternative "mitochondrial-friendly" NRTIs such as ABC and TDF, NRTI-sparing regimens based on PI/NNRTI combinations, or reinstitution of the offending NRTI at lower dosages have been successful in some patients.[158,159]

Asymptomatic hyperlactatemia

Asymptomatic, low-level increases in lactate are believed to not require intervention, as there is no conclusive evidence that asymptomatic lactate elevations are dangerous in the short term or predictive of more severe lactic academia.[160] The long-term consequences of low-level lactate elevation merit further investigation.

Because there is no way to predict who will develop lactic acidemia, patients on NRTI therapy should be made aware of the signs and symptoms of this syndrome and of the need to seek medical care promptly should these occur. A high index of suspicion is warranted specifically during episodes of infection, as antecedent minor, mainly respiratory, infections have been noted to precede cases of symptomatic lactic acidemia.[161]

Bone Disease

Osteonecrosis

Background and definition

Osteonecrosis or avascular necrosis is defined as bone tissue death as a result of compromised blood flow to bone. Osteonecrosis had been reported in the setting of HIV infection even prior to the availability of potent ART.[162-164] Affected bones included the femoral head and condyle, humeral head, proximal tibia, and bones of the hand and wrist. Interruption of the vascular supply to bone results in a stepwise progression through ischemia, hyperemia, an increase in intraosseous pressure, and eventually death of osteocytes. Osteonecrosis usually affects bone closest to the joint space. Imaging studies reveal subchondral lucency followed by the collapse of bone and narrowing of the joint space. In a cross-sectional study of HIV-positive outpatients in San Francisco, MRI detected evidence of osteonecrosis in 4.4% of 339 asymptomatic patients surveyed, compared with 0.02% to 0.14% in the general population.[165] Osteonecrosis has been seen predominantly in patients with advanced HIV disease and in males between the ages of 20 and 50 years, with the majority of affected patients having at least one risk factor previously associated with osteonecrosis in the HIV-uninfected population.[166-168] Common risk factors in the general population include use of systemic corticosteroids, ethanol abuse, hyperlipidemia (particularly hypertriglyceridemia), hypercoagulable states, hemoglobinopathies, autoimmune disorders, pancreatitis, pregnancy, heavy weight bearing, trauma, and osteomyelitis.[169]

Mechanism(s) of disease

Osteonecrosis involves the death of bone tissue through vascular compromise. The exact mechanism of this vascular occlusion is not known.[170] A possible mechanism of osteonecrosis is the development of vasculitis and thrombosis resulting in disruption of the vascular endothelium and luminal occlusion.[169]

HIV infection has been associated with the development of anticardiolipin antibodies, which have been reported to occur in 50% to 86% of the HIV-positive population in a cross-sectional study.[171] Deficiency of the antithrombotic factor protein S has been associated with HIV infection and may result in thrombotic events.[171] Several case-control studies in HIV-positive subjects have associated corticosteroid use with osteonecrosis.[165,167,172] Patients with osteonecrosis also tend to have histories of more severe immunosuppression and a higher BMI compared with controls.[173] Hyperlipidemia and alcohol use, rather than any specific antiretroviral agent, have also been associated with osteonecrosis.[167] Based on available studies, there is little evidence to suggest that ART is directly involved with the development of osteonecrosis.[173]

Diagnosis and therapy

The International AIDS Society-USA Panel does not recommend routine screening of HIV-positive patients for the presence of osteonecrosis. A high index of suspicion is warranted, however, in patients who present with pain over the joints or bone. Magnetic resonance imaging is the most sensitive and specific imaging technique for early detection of osteonecrosis and is indicated if plain films are normal and symptoms of osteonecrosis persist.[172] Early detection of this disease can help reduce its extent and morbidity. The same principles for management of osteonecrosis as those for treating HIV-negative patients should be followed.[172] Bone pain can be treated with nonsteroidal anti-inflammatory drugs. Surgical resection with joint replacement is the only effective therapy for the treatment of symptomatic osteonecrosis.[170] Physical therapy can help retain functionality. Discontinuation of all corticosteroids and abstinence from alcohol and smoking may be indicated.

Glucocorticoids are prescribed for various conditions associated with HIV. Because there are studies suggesting that even the short-term use of glucocorticoids may predispose patients to osteonecrosis, these agents should be used judiciously, in the lowest effective dosages, and for the shortest possible length of time.

Osteopenia and osteoporosis

Background and definition

Osteopenia refers to bone demineralization, and osteoporosis refers to bone demineralization of sufficient significance that it is likely to lead to or be associated with fractures after minimal trauma. A more specific classification has been devised,[174,175] using four diagnostic categories related to bone mineralization: Normal, Osteopenia, Osteoporosis, and Established Osteoporosis with Fragility Fractures. The classification relies on the use of DEXA scanning, typically of the hip and spine, to determine bone density. The DEXA results are reported in absolute terms (g/m^2) and in relative terms: T-score and Z-score. The T-score is the number of standard deviations between the obtained result and the value expected in a young individual at peak bone density (25 to 30 years old). The Z-score represents the number of standard deviations between the obtained result and an age, ethnicity, and gender-matched average value from healthy patients. Osteopenia is defined as a T-score between one and 2.5 standard deviations below the average found in young people. Osteoporosis is a T-score >2.5 standard deviations below the average found in young people. Established osteoporosis is a T-score >2.5 standard deviations below the mean in the presence of fragility fractures.

Osteopenia and osteoporosis occur at high frequency in the HIV-positive population on ART compared with age-matched, HIV-negative controls. Observational studies have reported higher rates of osteopenia in patients having CD4 counts ≤100 cells/μL (45%), patients taking PIs (50%), and those with evidence of lipodystrophy (28%).[176,177] These same studies found osteoporosis to occur in 40% of those with a CD4 count ≤100 cells/μL, 21% in those taking PIs, and 9% of those with lipodystrophy. An association of osteopenia with lactic acidemia also has been found.[178] However, despite the high prevalence of bone demineralization, a greater-than-expected occurrence of fragility fractures has not been documented. The accelerated bone loss observed during ART does not appear to be progressive beyond the period immediately after ART initiation.[179]

Mechanism(s) of disease

In ART-naive patients, there is a significant increase in bone resorption and a decrease in bone formation compared with seronegative controls.[180] Although a role for cytokine-mediated bone resorption has been demonstrated, the initiation of ART appears to be the greatest contributor to bone demineralization.[181] Patients receiving potent ART have increased bone alkaline phosphatase and osteocalcin, which are markers of bone turnover.[181] Protease inhibitor use has been associated with increased osteocalcin, suggesting a possible mechanism for bone demineralization.[181] Although some PIs may block the differentiation of osteoblasts, thereby reducing the rate of new bone formation, recent longitudinal studies have shown a smaller contribution of PIs to osteopenia and osteoporosis.[182] Switching from a PI-based regimen to an NNRTI-based one does not result in improvements in bone mineral density.[179] Gilead Study 903 found TDF to have the greatest bone-demineralizing effect among antiretroviral agents.[183]

Diagnosis

As with its approach to osteonecrosis, the International AIDS Society-USA Panel does not recommend routine screening for the presence of osteopenia or osteoporosis.[1] However, recommendations may change as more information becomes available regarding the prevalence of osteoporosis in this population, its association with fracture risk, and safety and efficacy of various modalities for therapy. In the general population, routine DEXA scans are now recommended by the US Preventive Task Force in all women above age 65 and selected women in the 60 to 65 age range, because of the increased prevalence of osteopenia and osteoporosis in these groups.[174,184] In the HIV-positive population, until more information is available, it may be reasonable to conduct screening DEXA scans for those at high risk for fragility fractures. Risk factors for fragility fractures include duration of HIV infection, low BMI, history of weight loss, previous use of corticosteroids, smoking, excessive alcohol intake, inactivity, and history of inadequate calcium intake.[179,185]

Therapy

Osteopenia is usually asymptomatic. Patients suffering from severe osteoporosis may present with pain over the joints or bones as a result of one or more fractures. Current therapies used to treat

bone demineralization have not been studied completely in the HIV-positive population and are extrapolated from recommendations in the general population. Complicating the decision to initiate therapy for osteoporosis is the finding that the observed bone demineralization does not appear to be rapidly progressive beyond the period immediately after ART initiation.[179] The goal of therapy, as in the elderly population, is to reduce fractures and maintain function. Accordingly, initiation of therapy for osteopenia and osteoporosis should be tailored to individual risk for future fragility fractures. Lifestyle modifications generally accepted as part of the overall reduction of bone demineralization include increased physical activity, weight loss, and smoking cessation. Patients diagnosed with osteopenia or osteoporosis should consume 1,500 mg of calcium and 400 to 1,000 international units of vitamin D daily. Bisphosphonates, such as alendronate, which function by retarding bone resorption, have been effective in treating osteoporosis in the general population and are the only FDA-approved treatment of osteoporosis in men. The safety and efficacy of bisphosphonates in the treatment of osteopenia and osteoporosis in HIV-positive patients has been demonstrated in a small number of prospective studies.[186,187] A larger randomized multicenter trial examining the use of alendronate is under evaluation (Adult ACTG A5163). The use of raloxifene, a selective estrogen receptor modulator, may be contraindicated because of its inhibition of cytochrome P450 and potential drug interactions with ART. ■

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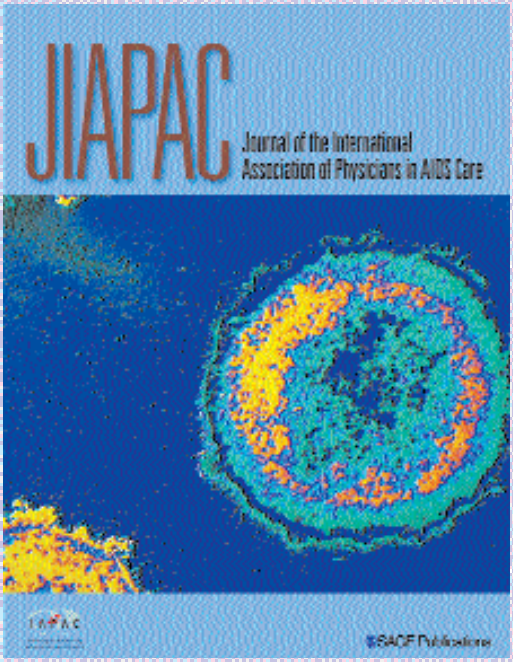

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Time to Deliver • Passons aux actes

Editor's Note: *Following are selected abstracts from the XVI International AIDS Conference, held August 13-18, 2006, in Toronto.*

Complications of Antiretroviral Therapy

Abstract MOAB0304: Increasing rates of community-acquired MRSA infections among HIV-infected persons

Crum-Cianflone N, Hale B, Burgi A, et al, and the TriService AIDS Clinical Consortium.

BACKGROUND: Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) rates are rapidly increasing in the general population, but there are few data regarding the rates among HIV-infected patients and the risk factors in this population. *METHODS:* We assessed the incidence of CA-MRSA infections from 1993 to 2005 in a large HIV clinic. We collected data on all patients with CA-MRSA infections receiving care at our facility. Cases were defined as patients with a positive MRSA culture without a history of recent (within one year) hospitalization. We compared HIV patients with MRSA to HIV patients without MRSA in terms of demographics, antibiotic and antiretroviral history, CD4 counts, viral loads, and STDs using Fisher's exact and rank-sum testing. A backward stepwise multivariate logistic regression model was constructed to determine risk factors for CA-MRSA. *RESULTS:* Among 425 HIV patients, 25 (5.9%) developed CA-MRSA. All cases occurred after 2002, with a 17-fold increase from 2003 to 2005 (chi-square test of trend 15.7, $P < 0.001$). The annual incidence in 2005 among HIV patients was 40 cases/1,000 person-years compared to 741 cases/325,000 (or 2.28/1,000) person-years among HIV-negative persons (18-fold higher rate). All HIV-infected patients developed soft-tissue infections, 16% required hospitalization, 67% had a positive nares culture, 0% were taking Septra prophylaxis, and 56% HAART. Sixteen percent had relapsing MRSA infections despite appropriate initial antibiotics. In the univariate analyses, lower current CD4 count, CDC stage C, history of syphilis, and B-lactam antibiotics in the past year were predictive of MRSA; there were no associations with demographics, diabetes, or HAART. In the multivariate analysis, recent use of B-lactam antibiotics ($P = 0.04$) and syphilis ($P = 0.02$) predicted CA-MRSA infections in HIV patients. *CONCLUSIONS:* Community-acquired MRSA infections are rapidly increasing among HIV-infected patients. HIV patients have an 18-fold higher risk for CA-MRSA than the general population. Risk factors for CA-MRSA include recent use of B-lactam antibiotics and high-risk sexual activity as demonstrated by syphilis infection.

Abstract MOPE0219: Potential health risks of complementary alternative therapy (CAM) in HIV-positive patients taking antiretroviral (ARV) drugs

Ladenheim D, Phillpot M, Horn O, et al.

BACKGROUND: Use of CAM in patients with HIV or AIDS can be a major concern, since many CAMs may interact with antiretroviral therapy, thereby potentially compromising its effectiveness. The aim of this study was to investigate the prevalence of CAM use in patients taking antiretroviral therapy in three specialist HIV outpatient clinics. We determined the frequency of any potentially serious interactions, relative or absolute contraindications, and warnings issued when potential health risks were identified. *METHODS:* Cross-sectional survey of a random sample of patients taking ARV drugs, using a multiple choice questionnaire exploring use of herbal remedies, supplements, and physical complementary treatments. If potential for significant interactions with ARV drugs or for other adverse effects was identified, a warning was issued. *RESULTS:* Two hundred fifty-three patients were included in the study. Of these, 154 (60.9%) were taking herbal remedies or supplements and 88 (34.8%) were using physical treatments. Sixty-seven patients (26.5%) used a combination of both. Twenty-five (9.9%) were asked to stop their CAM because of potentially serious drug interaction with their antiretroviral therapy, or adverse effects of the remedy used. Thirty patients (11.9%) were advised to use their remedies with caution and adequate monitoring. Of those taking CAMs, 51.3% had discussed CAM use with a health care professional. *CONCLUSIONS:* Our study suggests that the prevalence of CAM use in UK HIV-positive patients is comparable to that seen in other countries. Ten percent of patients in our cohort were potentially seriously compromising their ARV treatment by taking CAMs. Medical practitioners need to be able to identify CAM use in HIV-positive patients and recognize associated potential health risks. Equally, patients should be encouraged to disclose CAM use to their clinicians.

Coinfection with Tuberculosis

Abstract MOAB0104: Tuberculosis incidence and risk factors among adult patients receiving HAART in Senegal: A seven-year cohort study

Diouf A, Etard J-F, Ndiaye I, et al.

BACKGROUND: Tuberculosis is a leading cause of death among HIV-1 infected adults receiving highly active antiretroviral therapy (HAART) in Senegal. *METHODS:* Tuberculosis incidence was assessed in the patients enrolled between August 1998 and April 2002 in the Senegalese antiretroviral drug access initiative. Patients were included according to the consensus reports on HAART in Africa issued in 1997 and 2000. First-line regimens combined two NRTIs and either an NNRTI or a PI. Follow-up visits were done every two months with a complete biological assessment every six months. Cases of tuberculosis were ascertained by examining the patient clinical files. Survival analyses were performed. *RESULTS:* Three hundred ninety-seven patients (54.7% women) were enrolled in the study and were followed for a median of 46 months (interquartile range: 32 to 57 months) after HAART initiation for a total of 1,403 person-years as of September 30, 2005. At baseline, 5% were not antiretroviral therapy-naive, 39% and 55% were respectively at CDC stage B and C; median age, CD4 count, and viral load were respectively 37 years, 128 cells/µL, and 5.2 log copies/mL. More than one fourth of the patients had a previous history of tuberculosis, and 47 incident cases of tuberculosis

were recorded after HAART initiation, yielding an overall incidence rate of 3.2/100 person-years (95% confidence interval [CI] 2.4 to 12.4). The incidence rate decreased with time after starting HAART from 6.4 per 100 person-years (4.2 to 9.6) for the first year to 3.5 per 100 person-years (1.9 to 6.3) for the second year and 1.4 per 100 person-years (0.5 to 3.7) for the third year. Incidence of tuberculosis was associated with anemia at baseline (hemoglobin level < 10 g/dL). *CONCLUSIONS:* This study provides the first estimates of tuberculosis incidence following HAART initiation in Senegal.

Abstract THLB0210: High prevalence and mortality from extensively drug-resistant (XDR) TB in TB/HIV-coinfected patients in rural South Africa

Gandhi NR, Moll A, Pawinski R, et al.

BACKGROUND: In a rural district in KwaZulu Natal, South Africa, where the TB/HIV coinfection rate is greater than 80%, antiretroviral therapy (ART) has significantly reduced mortality. Of the remaining deaths, 67% have been documented to be due to multi-drug resistant (MDR) TB. We sought to determine the extent and consequences of MDR TB among patients in this district. *METHODS:* Surveillance with sputum culture and drug susceptibility testing was performed for patients with known or suspected TB in a rural district hospital. Spoligotyping was performed on isolates resistant to all tested TB drugs (isoniazid, rifampin, ethambutol, streptomycin, ciprofloxacin, kanamycin). *RESULTS:* Between January 2005 and March 2006, sputum collected from 1,540 patients revealed that 536 (35%) patients were culture-positive for *M. tuberculosis*. Of these, 221 (41%) had MDR TB, and 53 (24% of MDR isolates, 10% of all positive cultures) had resistance to all first- and second-line drugs tested (XDR TB). Spoligotyping revealed 90% of XDR TB patients were infected with a genetically similar strain. Fifty-two of 53 (98%) XDR TB patients have died; the median survival after sputum collection was 25 days (range: 11 to 136). All 47 XDR TB patients with known HIV status were HIV-positive. Only 34% of patients were previously treated for TB and 56% had been previously hospitalized. *CONCLUSIONS:* Increased surveillance in rural South Africa revealed a markedly greater MDR TB prevalence than previously recognized, with evidence of recent nosocomial and community transmission of XDR TB in HIV-coinfected patients. The convergence of the TB/HIV epidemic with MDR and XDR TB in resource-poor settings is a deadly threat to gains in survival achieved by TB directly observed therapy (DOTS) and ARV therapy.

Scaling Up Antiretroviral Therapy in Developing Countries

Abstract MOAB0401: A pilot randomized trial of nutritional supplementation in food-insecure patients receiving antiretroviral therapy (ART) in Zambia

Megazzini K, Washington S, Sinkala M, et al.

BACKGROUND: In many parts of sub-Saharan Africa, where the need for ART is most urgent, there is also widespread hunger. Whether food supplementation can improve clinical and adherence outcomes of food-insecure populations on ART has been widely debated, but not yet tested. *METHODS:* In the context of a home-based adherence support program attached to eight government clinics in Lusaka, we randomly assigned four clinics to provide a monthly household food ration (micronutrient-fortified corn-soya blend, from the World Food Programme) to food-insecure patients starting ART; four clinics served as controls. Weight and CD4 change were measured at six and 12 months. Adherence was assessed by timeliness of pharmacy visits. *RESULTS:* At baseline, the median age, body mass index (BMI), CD4 count, WHO stage, hemoglobin, or gender distribution did not differ significantly between 375 food recipients versus 161 non-recipients. For those receiving food, the median number of rations received was nine (interquartile range [IQR]: 6 to 10); median time between starting ART and first ration was 70 days (IQR: 44 to 125). We observed negligible differences in weight gain (kg) at six months (+5.6 versus +5.0; $P = 0.48$) and 12 months (+6.2 versus +5.5; $P = 0.44$) between food recipients and non-recipients. However, food recipients had a substantially greater increase in CD4 count at 12 months than did non-recipients (+185 versus +113; $P = 0.017$). The mean number of days late for pharmacy visits per month was lower among food recipients versus non-recipients (2.4 versus 3.4; $P = 0.008$). Both the CD4 and adherence findings remained statistically significant in multivariate analyses adjusting for sex, WHO stage, and BMI at entry. *CONCLUSIONS:* In this pilot study, a monthly household food ration for food-insecure patients commencing ART improved adherence by 40% and resulted in a better CD4 response at 12 months of therapy. Further study is warranted of food supplementation as an adjunct to ART in food-insecure patients.

Antiretroviral Therapy

Abstract THPE0145: The effect of episodic CD4-guided antiretroviral therapy on quality of life: Results of the quality of life substudy of SMART

Burman W, for the SMART Study Group.

BACKGROUND: The SMART study is an international, randomized trial with 5,472 participants comparing an episodic CD4-guided antiretroviral treatment (ART) strategy (drug conservation [DC] arm) with continuous ART (viral suppression [VS] arm). It was hypothesized that episodic ART might improve quality of life (QOL) by reducing time spent on ART. *METHODS:* A subset of SMART study participants enrolled in 64 US sites had QOL assessments (current health state, assessed by visual analog scale, and SF-12) at baseline, months four, eight, and 12, and annually thereafter. The DC and VS strategies were compared longitudinally for changes in the visual analog scale, each of the eight SF-12 dimensions, and physical (PCS) and mental (MCS) health components. *RESULTS:* Of 1,225 patients participating in the substudy, most (76%) were on ART at enrollment, 25% were women, and median CD4 count was 575 (interquartile range [IQR] 455 to 784) cells/mm^3. At study entry, mean current state of health scores was 75 (out of 100). Fifty percent rated their health as very good or excellent on the SF-12 general health question. Mean follow-up was 2.4 years. During follow-up, current health state and general health perception declined in the DC group and increased in the VS group ($P = 0.09$ for difference in current state of health and $P = 0.02$ for general health perception). Drug conservation patients also scored lower on the physical summary score (PCS; $P = 0.005$) and in the energy dimension of the SF-12 (baseline = 60 out of 100 and average change of -1.7 versus +0.2; $P = 0.05$). Differences in other SF-12 dimensions and the MCS between groups were small and not statistically significant. *CONCLUSIONS:* Episodic use of ART as in SMART did not improve quality of life. Physical functioning, general health perception, and energy scores worsened among patients in the DC group compared to the VS group.

Abstract WEAB0203: Progression of HIV-related disease or death (POD) in the randomized SMART study: Why was the risk of POD greater in the CD4-guided ([re-]initiate ART at CD4 < 250 cells/μL) drug conservation (DC) versus the virological suppression (VS) arm?

Lundgren JD, on behalf of the SMART Study Group.

BACKGROUND: The SMART study ($n = 5,472$) demonstrated a 2.5-fold greater risk of POD in the DC versus VS arm. Factors associated with this finding are reported here. *METHODS:* The POD event ($n = 164$) rates were calculated based on the proximal CD4 cell and HIV-RNA viral load (VL) levels. Cox models assessed whether these levels affected the difference between arms in risk of POD and determined independent risk factors for POD in each arm. *RESULTS:* The median and interquartile range (IQR) of the proximal CD4 count prior to diagnosis of PODs was 333 cells/μL (246 to 488) and 512 cells/μL (328 to 651) in the DC and VS arms, respectively. The rate of POD was higher for lower strata of proximal CD4 counts and for higher strata of VL levels in both arms, but higher in DC versus VS arm for CD4 count >350 cells/μL and VL <3.5 $\log_{10}$ copies/mL (Table 1). Per design, in the DC arm, more time was spent with lower CD4 and higher VL levels. Risk of POD in the DC arm was associated with lower proximal CD4 counts and older age; higher proximal VL levels and older age predicted risk in VS arm. The hazard ratio (DC/VS) for POD was reduced from 2.5 ($P < 0.001$) to 1.4 ($P = 0.12$) after adjustment for proximal CD4 and VL levels. Patients in DC arm (re)-initiated ART at protocol-specified CD4 levels (232 cells/μL [192 to 299]), and achieved good CD4/VL responses (eg, median time to VL < 400 copies/mL = three months; 142 CD4 cells/μL increase after eight months); POD rates were similar for three four-month intervals following ART initiation: 5.1/100 PY, 5.3/100 PY, and 5.7/100 PY. *CONCLUSIONS:* Intended differences in proximal CD4 and VL levels between the arms of the study explains a substantial part of the

Table 1. **Rates (/100 PY) according to proximal CD4 and HIV RNA levels (% of total follow-up time in arm) (Abstract WEAB0203)**

	Proximal CD4 count (cells/muL)				*Proximal HIV RNA (Log10 copies/mL)*			
Study arm	<250	250-349	350-499	>499	<2.3	2.3-3.5	3.5-4.5	>4.5
DC	12.4 (8%)	4.1 (23%)	2.6 (34%)	2.5 (35%)	4.3 (21%)	2.6 (16%)	2.6 (35%)	5.2 (28%)
VS	13.7 (2%)	3.9 (6%)	1.1 (22%)	1.1 (70%)	0.8 (68%)	1.8 (17%)	3.0 (10%)	5.7 (5%)

difference in the risk of POD between the DC and VS arms. Additional analyses on predictors of POD will be presented.

Abstract TUAB0103: 48-week efficacy and safety results of simplification to single agent lopinavir/ritonavir (LPV/r) regimen in patients suppressed below 80 copies/mL on HAART—the KalMo study

Nunes EP, Oliveira MS, Almeida MMTB, et al.

BACKGROUND: Long-term adverse events and expense associated with highly active antiretroviral therapy (HAART) have led to an interest in simplified therapy. Lopinavir/ritonavir monotherapy is attractive due to its potency and high genetic barrier. *METHODS:* This is a 48-week interim analysis of a 96-week, open-label, randomized study to assess the feasibility of using LPV/r monotherapy in patients with undetectable viral load after being on HAART for at least six months, and without previous virologic failure. Subjects were randomized (1:1) to either switch from triple HAART to LPV/r monotherapy or to maintain their current triple HAART regimen. *RESULTS:* Sixty patients were enrolled. Baseline characteristics were similar in both groups. At week 48, by intention-to-treat analysis, 26 of 30 (86.7%) subjects in the monotherapy arm and 25 of 30 (83.3%) subjects in the control group had a viral load (VL) of <80 copies/mL. There was one virologic failure (VF) (defined as VL >1,000 copies/mL) in each arm. One subject in the monotherapy arm experienced VF with a VL of 1,200 copies/mL at week 48. Genotypic resistance results are pending; however, this subject was intensified with tenofovir (TDF) + lamivudine (3TC) at the time of VF and subsequently re-suppressed to <80 copies/mL. One subject in the control arm experienced VF at week 36. Resistance testing showed no resistance-associated mutations. No statistically significant differences were found with regard to changes in CD4 counts, serum cholesterol, and anthropometric measures. There were no grade 3 or 4 lab abnormalities observed. One subject in the monotherapy group discontinued due to diarrhea. Two subjects in the control group underwent regimen changes due to drug-related toxicities. *CONCLUSIONS:* Switching from various triple HAART regimens to LPV/r monotherapy, in patients who were virologically suppressed and without a history of previous virologic failure, was effective, safe, and well tolerated through 48 weeks.

Abstract MOPDB06: Very low CD4 T-cell counts and low total lymphocyte counts at initiation of HAART are associated with a poor outcome in the first six months of antiretroviral treatment

Mayanja-Kizza H, Lutwama F, Kamya M, et al.

BACKGROUND: Global highly active antiretroviral therapy (HAART) scale-up efforts have increased access to AIDS treatment in developing countries, but mortality remains high despite adequate management. *METHODS:* A cohort of 550 patients starting HAART was prospectively followed up over 30 months at an AIDS treatment center in Kampala, Uganda. Regular clinical review and CD4 and viral load counts were done every three and six months, respectively. Early home visits to locate those who missed clinical appointments were done. Data was compared to patients alive after more than 12 months of HAART. *RESULTS:* Seventy-two (13%) patients (45 females, mean age 36.7 [standard deviation (SD) 19] and 27 men, 39.3 [SD six] years), died while on antiretroviral (ARV) drugs despite over 90% adherence. Twenty-nine died within six months of commencement of ARV drugs, 24 between six and 12 months, and 19 died after one year. Highly active antiretroviral therapy was started at very low CD4 counts, with a median 24 cells/mm^3 among those who died, (for deaths within six, six to 12, and over 12 months of HAART, median CD4 counts were 14 cells/mm^3, 31 cells/mm^3, and 73 cells/mm^3, respectively) compared to 110 cells/mm^3 among over-12-month survivors (P = 0.002). Initial total lymphocyte counts were significantly lower among patients who died within six months (mean 1,200 cells/mm^3 [SD 720]) compared to deaths over one year (1,800 cells/mm^3, [SD 1,038]) and survivors (1,780 cells/mm^3 [SD 1,120]) (P = 0.028). Viral load at onset of HAART was similar in all groups, with a mean of 5.5 logs among survivors and 5.7 logs among all deaths. There was better viral load suppression at 12 months, with 2.9 logs among survivors, compared to 0.4 log among people who died over one year (P = 0.005). *CONCLUSIONS:* High mortality on HAART may be associated with late commencement of treatment at very low CD4 counts, where despite adequate treatment immune recovery lags behind virological suppression. Commencing HAART at earlier CD4 counts should be considered, even in resource-limited countries, to improve outcome.

Abstract WEAB0302: 3TC + ABC maintains virological superiority over ZDV + 3TC and ZDV + ABC beyond five years in children: The PENTA 5 trial

Gibb DM, Green H, Saidi Y, et al, on behalf of PENTA 5.

BACKGROUND: PENTA 5 was a 48-week randomized controlled trial comparing three dual nucleoside reverse transcriptase inhibitor (NRTI) combinations with or without nelfinavir (NFV) as first antiretroviral therapy (ART). We describe long-term response to five years. *METHODS:* One hundred twenty-eight ART-naive children were randomized to zidovudine (ZDV) + lamivudine (3TC) (n = 36), ZDV + abacavir (ABC) (45), or 3TC + ABC (47). Asymptomatic children (n = 55) were also randomized to NFV or placebo; all other children received open-label NFV. One child was lost to follow-up and one died before two weeks, leaving data on 126 children with follow-up. Analyses are intent-to-treat and adjusted for minor baseline imbalances and receipt of NFV/placebo. *RESULTS:* Median follow-up was 5.8 years (interquartile range [IQR] 5.2 to 6.5). By five years, 17 (47%), 27 (61%), and 18 (39%) children had changed their randomized NRTIs in the ZDV + 3TC , ZDV + ABC, and 3TC + ABC arms respectively, but 18%, 48%, and 50% of these changes were either early single drug substitutions for toxicity or switches in children with viral suppression (plasma HIV-1 RNA viral load [VL] <400 copies/mL; eg, for simplification). Of 105 children with VL at year five, 55%/32% ZDV + 3TC , 50%/25% ZDV + ABC, and 79%/63% 3TC + ABC had VL <400/<50 copies/mL respectively (P = 0.03/P = 0.003). Corresponding decreases in $\log_{10}$ VL were 2.5, 2.5, and 3.6 respectively (P = 0.001). Mean increases in CD4 percentage were 14%, 10%, and 12% (P = 0.2); height for age 0.24, 0.39, and 0.79 (P = 0.02); and weight for age 0.19, 0.18, and 0.81 (P = 0.02). Reverse transcriptase resistance mutations differed between the arms: ZDV + 3TC (41, 184, 210, and 215); ZDV + ABC (67, 215); and 3TC + ABC (65, 74, 115, and 184). Of the 24 children randomized to dual NRTIs only, zero of seven taking ZDV + 3TC , three of 11 taking ZDV + ABC, and four of six taking 3TC + ABC were still taking only two drugs at year five (zero, one, and three with VL <400 copies/mL). *CONCLUSIONS:* Improved efficacy, in terms of VL suppression and growth changes, and lower rates of switching with detectable VL in the 3TC + ABC arm were sustained through to year five.

Abstract TUAB0102: Long-term clinical and immunologic outcomes are similar in HIV-infected persons randomized to NNRTI versus PI versus NNRTI + PI-based antiretroviral regimens as initial therapy: Results of the CPCRA 058 first study

MacArthur RD, Novak RM, Peng G, et al, for the CPCRA 058 Study Team and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA).

BACKGROUND: Clinical outcomes data are lacking on the long-term consequences of initiating therapy with a protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI), or both. *METHODS:* Between 1999 and 2002, 1,397 treatment-naive persons were randomized 1:1:1 to 1) PI + nucleoside reverse transcriptase inhibitors (NRTIs), 2) NNRTI + NRTIs, or 3) PI + NNRTI + NRTI(s). Primary endpoints were a composite of AIDS events, death, and CD4 count decline to <200 cells/mm^3 (PI versus NNRTI comparison); and CD4 count change after 32 months (three-class versus combined two-class comparison). *RESULTS:* Median age was 38 years; 21% were female; 54% were black, 17% were Latino. Median CD4 count was 163 cells/mm^3. Median follow-up was five years. Three hundred and two persons developed an AIDS event or died; 188 died; 388 developed the composite clinical/CD4 count endpoint. Nonnucleoside reverse transcriptase inhibitor versus PI hazard ratios (HRs) for the composite endpoint, AIDS or death, and virologic failure (VF) (HIV RNA >1,000 copies/mL after four months) were 1.02 (95% confidence interval [CI]: 0.79-1.31), 1.07 (0.80-1.41), and 0.66 (0.56-0.78), respectively. Mean increases in CD4 counts after 32 months were 227 and 234 cells/mm^3 for the combined two-class and three-class strategies (P = 0.62), respectively. Hazard ratios (three-class versus combined two-class strategies) for AIDS or death and VF were 1.14 (95% CI: 0.91-1.45) and 0.87 (0.75-1.00), respectively. Hazard ratios (three-class versus combined two-class strategies) for AIDS or death and VF were similar for persons with baseline CD4 counts <200 and >200 cells/mm^3 (P = ns for interaction). Persons assigned to the three-class arm discontinued therapy due to toxicity more than those assigned to the two-class arms (HR = 1.58, P < 0.01). *CONCLUSIONS:* Nonnucleoside reverse transcriptase inhibitor-based and PI-based strategies for initial therapy do not differ for a composite outcome based on CD4 count decline, AIDS events, and death after a median follow-up of five years. The NNRTI strategy was superior virologically to the PI-based strategy. A three-class strategy is not superior to a two-class strategy for immunologic or clinical outcomes, and is associated with more drug toxicity.

Abstract WEAB0305: Nevirapine concentrations in HIV-infected children treated with divided fixed-dose combination tablets in Malawi and Zambia

Mulenga V, Ellis J, Ewings F, et al.

BACKGROUND: Some African HIV-infected children are treated with divided fixed-dose combination (FDC) Triomune® (stavudine [d4T] + lamivudine [3TC] + nevirapine [NVP]) tablets. There are few data on NVP pharmacokinetics in such children, in whom malnourishment is common. *METHODS:* Steady-state plasma NVP concentrations were determined in 127 HIV-infected children aged three months to 16 years, who had received Triomune® in Malawi or Zambia. Center-stratified regression with backwards elimination ($P > 0.1$) was used to identify predictors from height for age, BMI for age, age, sex, post-dose sampling time and dose/m^2/day. *RESULTS:* The 71 Malawian children were similar in age (median 8.4 years), but more malnourished (BMI for age -0.89, height for age -3.15) and had longer post-dose sampling times 8.9 hours) than the 56 Zambian children (8.9 years, -0.50, -1.84, 3.5 hours respectively). Median interquartile range (IQR) NVP levels were 4.8 (2.8, 6.5) [0.15, 15.4] and 7.0 (5.4, 10.5) [0.15, 17.1] mg/L in Malawian and Zambian children respectively. Only those on a nearly adult dose (350 to 400 mg NVP/day) received the target dose of 300 mg/m^2/day (median 337 mg/m^2 [IQR 303 to 366] [range 274 to 454], 2% < 3 mg/L [considered subtherapeutic]); those prescribed 50 to 200 mg/day (quarter/half tablets) were more frequently underdosed (236 mg/m^2 [217 to 267] [120 to 354], 21% <3 mg/L), as were those prescribed >200 mg to <350 mg (263 mg/m^2 [260 to 271] [245 to 292], 21% <3 mg/L). Lower height for age (indicating stunting) (+0.37 mg/L per unit higher [95% CI -0.013 to +0.75], $P = 0.06$), lower prescribed dose/m^2 (+0.67 mg/L per 50 mg/m^2 higher [+0.014 to + 1.32], $P = 0.05$) and younger age (+0.15 mg/L per year older [-0.022, to +0.31], $P = 0.09$) were independently associated with lower NVP levels. There was no significant independent effect of lower BMI for age (indicating wasting) (-0.33 mg/L per unit higher [-0.76 to +0.09], $P = 0.12$), although this was a stronger predictor when restricted to Malawian children (-0.51 [-1.01 to -0.02], $P = 0.04$). *CONCLUSIONS:* To avoid NVP underdosing in young children, divided FDC Triomune® should be used with caution; NVP levels may be reduced in stunted but increased in wasted children. Further studies investigating these relationships are required.

Clinical Trials of New Drugs and Techniques

Abstract TUAB0104: TMC114 provides durable viral load suppression in treatment-experienced patients: POWER 1 and 2 combined week 48 analysis

Lazzarin A, Queiroz-Telles F, Frank I, et al.

BACKGROUND: In the POWER 1 (TMC114-C213) and 2 (TMC114-C202) 24-week primary analysis, TMC114 (darunavir or DRV) with low-dose ritonavir (DRV/r) demonstrated better antiviral activity than control protease inhibitors (CPIs) in treatment-experienced patients. The highest dose (600/100 mg bid) provided the greatest virologic response. The combined 48-week analysis of these trials assesses long-term efficacy and safety of DRV/r 600/100 mg bid versus CPIs. *METHODS:* In both trials, PI-, nucleoside reverse transcriptase inhibitor (NRTI)- and nonnucleoside reverse transcriptase inhibitor (NNRTI)-experienced patients with ≥1 baseline primary PI mutation were randomized to receive an optimized background regimen plus one of four DRV/r doses or a boosted CPI. Virologic response and adverse events (AEs) in patients initially randomized to DRV/r 600/100 mg bid and CPIs were compared at week 48 (intent-to-treat [ITT]/time to loss of virologic response [TLOVR]). The primary efficacy parameter was the proportion of patients with ≥1 $\log_{10}$ viral load reduction. *RESULTS:* At the recommended dose for treatment-experienced patients, DRV/r achieved significantly higher virologic response rates than CPIs at week 48, similar to those observed at week 24 (Table 2). The most commonly reported AEs during DRV/r 600/100 mg bid treatment were diarrhea (20%), nausea (18%), headache (15%), nasopharyngitis (14%), and fatigue (12%), reported in 28%, 13%, 20%, 11%, and 17% of CPI patients, respectively. The majority of AEs were grade 1 to 2 in severity. *CONCLUSIONS:* Darunavir/ritonavir has demonstrated sustained efficacy in this treatment-experienced population. Its tolerability profile is similar to that of CPIs, with a lower incidence of diarrhea.

Abstract THLB0215: Safety and efficacy of maraviroc (MVC), a novel CCR5 antagonist, when used in combination with optimized background therapy (OBT) for the treatment of antiretroviral-experienced subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial

Mayer H, van der Ryst E, Saag M, et al.

BACKGROUND: Maraviroc is a CCR5 antagonist active against R5 but not X4 or dual-tropic (R5/X4) HIV-1 *in vitro*. Patients with "dual-tropic" HIV generally are infected with a mixture of virus populations comprising R5, X4, and R5/X4 variants. This study was performed to determine the safety and efficacy of MVC, added to an optimized regimen versus OBT alone, in patients with dual/mixed-tropic (D/M) infection. *METHODS:* A4001029 is an ongoing, double-blind, placebo-controlled trial. Subjects on a stable antiretroviral regimen, with non-R5 virus, HIV-1 RNA 5,000 copies/mL, and triple-class experience and/or dual-class resistant virus were randomized to one of three groups: OBT ± MVC qd or bid. The primary endpoint was the change from baseline to 24 weeks in viral load (VL) for patients with D/M virus at screening, using an intent-to-treat analysis. *RESULTS:* Of 186 subjects with non-R5 virus randomized and treated, 167 had D/M virus at screening. Median baseline CD4 count was <50 cells/mL and mean baseline VL was >5 $\log_{10}$ copies/mL for each treatment group. Viral load change from baseline to week 24 was similar for the MVC qd (-0.91 $\log_{10}$) and placebo groups (-0.97 $\log_{10}$) but slightly greater for the MVC bid group (-1.20 $\log_{10}$). Mean CD4 change was greater for the MVC groups: +60 and +62 cells/L, for qd and bid, respectively, compared to +35 cells/L for placebo. Grade 3/4 adverse events, discontinuations, and deaths occurred with similar frequency in all three groups. There were no cases of lymphoma or adenocarcinoma. *CONCLUSIONS:* Maraviroc was safe and well tolerated in this advanced population with documented D/M HIV-1 infection. While superiority of either MVC dose added to OBT, versus OBT alone, was not achieved, there was no evidence of virological or immunological decline. In fact, a greater CD4 increase occurred in both MVC groups versus the placebo group, which requires further investigation.

Table 2. **Pooled POWER 1 and 2 virologic response rates (Abstract TUAB0104)**

	Week 24			Week 48		
Efficacy parameter	*DRV/r 600/100 mg bid (n = 131)*	*CPI (n = 124)*	*P-value*	*DRV/r 600/100 mg bid (n = 110)*	*CPI (n = 120)*	*P-value*
Patients with HIV RNA ≥1.0 $\log_{10}$ reduction (%)	70	21	<0.001	61	15	<0.001
Patients with HIV RNA <50 copies/mL (%)	45	12	<0.001	46	10	≤0.003
Mean HIV RNA $\log_{10}$ reduction (copies/mL)	–1.89	–0.48	<0.001	–1.63	–0.35	<0.001
Mean CD4 increase (cells/mm^3)	92	17	<0.001	102	19	≤0.005

Abstract TUPE0147: A nonrandomized large prospective evaluation of alternative injection devices (Biojector® 2000 [B2000], standard needles/syringes, or insulin needles/syringes) for enfuvirtide (ENF) in a national community-based specialty pharmacy

Tschida S, Zappa A, Godwin M.

BACKGROUND: Enfuvirtide-associated injection site reactions (ISRs) occur frequently and contribute to delayed ENF initiation and/or ENF discontinuation. Our objectives were to evaluate the impact of standard syringes, insulin syringes, or the B2000, a needle-free injection device, on ENF persistence, tolerability, and satisfaction. *METHODS:* Patients received the B2000 if they had moderate-to-severe ISRs, needle phobia, needle fatigue, or physical difficulty using syringes. Questionnaires assessing adherence, tolerability, and attitude/satisfaction were used at baseline, two weeks, and two, six, and 12 months. Persistency was calculated from ENF refills as the medication possession ratio (MPR). Comparisons between time points were carried out by the paired t-test for tolerability and attitude data and by the Wilcoxon signed rank test for satisfaction data. *RESULTS:* Of the 726 B2000 patients, 15.3% were ENF-naive, 78.2% continuing ENF, and 6.5% restarting ENF. Ninety-two percent (666/726) of ENF patients who started B2000 remain on ENF; primary reasons for discontinuing ENF included lack of virologic control (17/726, 2%) and ISRs (19/726, 3%). Eighty-five percent (616/726) of ENF patients who started B2000 continue on B2000; primary reasons for switching from B2000 included ISRs (22/726, 3%) and difficulty of use (12/726, 2%). Enfuvirtide adherence (following schedule most/all of time) for B2000 patients was 69%, 88%, and 85% at baseline, two weeks, and six months, respectively. Enfuvirtide persistency with B2000 was good; mean MPR 0.89. For patients that switched to B2000, pain and ISR symptoms were significantly improved from baseline ($P < 0.05$). Injection fear, concern, difficulty, and interference with daily activities were also significantly improved ($P < 0.05$). Of 172 patients evaluated at six months, 127 patients (74%) preferred B2000 to needles/syringes. Thirty-four

and 43 patients were using standard and insulin syringes, of which 2.9% and 11.6% discontinued ENF, respectively. *CONCLUSIONS:* The B2000 demonstrated high levels of persistency, tolerability, and patient satisfaction and represents an alternative to standard needle/syringe administration of ENF.

Abstract WEAB0301: Efficacy and safety results of 48 weeks of treatment with APTIVUS oral solution co-administered with low-dose ritonavir in children and teenagers (phase I/IIa study)

Salazar J, Cahn P, Della Negra M, et al, and PACTG 1051.

BACKGROUND: APTIVUS (tipranavir, TPV) is a recently approved protease inhibitor (PI), active against multi-PI resistant HIV. We report 48-week results of an open-label, international study of an investigational TPV oral solution co-administered with ritonavir (TPV/r) in children. Patients: 115 children (25 aged two to under six years, 38 six to under 12 years, 52 12 to 18 years; 97.4% antiretroviral [ARV]-experienced) were randomized, 58 to low-dose TPV/r (290/115 mg/m^2) and 57 to high-dose TPV/r (375/150 mg/m^2), plus an optimized background regimen (OBR). All patients commenced TPV solution; after four weeks, patients >12 years taking 500/200 mg could take capsules. *RESULTS:* Baseline mean viral load (VL): 4.7 $\log_{10}$ copies/mL; CD4 (CD4%): 492 cells/mm^3 (20%); median previous ARVs: six; genotypic resistance to all PIs: 49.6%. Thirteen percent of patients took enfuvirtide (ENF). Mean VL reductions at week 48 are shown in Table 3. At week 48, 39.7% (23/58) of low-dose patients and 45.6% (26/57) of high-dose patients achieved VL <400 copies/mL. And 34.5% (20/58) of low-dose patients and 35.1% (20/57) of high-dose patients achieved <50 copies/mL. At week 48, mean CD4 (CD4%) increased by 157 (5%) and 96 (3%) cells/mm^3 in low- and high-dose groups.

Table 3.

	Low-dose TPV/r	*High-dose TPV/r*
All patients	-1.34	-1.33
2 to <6 years	-2.46	-2.00
6 to <12 years	-1.27	-1.36
12 to 18 years	-0.83	-0.99

Tipranavir/ritonavir was well tolerated: four of 115 (3.5%) patients experienced drug-related serious adverse events (AEs). Ten patients (8.7%) (six low-dose; four high-dose) discontinued TPV/r because of AEs. Most common AEs were gastrointestinal. Most frequent Division of AIDS (DAIDS) grade 3/4 laboratory abnormalities were GGT and CPK increases (10.7%). *CONCLUSIONS:* Clinically relevant virological and immunological improvements were seen with TPV/r therapy in treatment-experienced children aged two to 18 years at week 48. Tipranavir/ritonavir provides a potent and well-tolerated therapeutic option for children and teenagers.

Abstract THLB0217: ACTG 5211: Phase II study of the safety and efficacy of vicriviroc in HIV-infected treatment-experienced subjects

Gulick R, Su Z, Flexner C, et al, for the ACTG 5211 Study Team.

BACKGROUND: Vicriviroc is an investigational CCR5 inhibitor with potent short-term antiretroviral activity. *METHODS:* Double-blind, randomized, 48-week study of vicriviroc in treatment-experienced patients taking ritonavir-containing regimens with R5-tropic virus (Monogram assay) and HIV-1 RNA (VL) >5,000 copies/mL. Vicriviroc at 5, 10, or 15 mg daily (or placebo) was given for 14 days; then background antiretroviral drugs were optimized. Virologic failure was defined as confirmed VL <1 $\log_{10}$ copies/mL below baseline at/after week 16; post-failure crossover to vicriviroc was permitted. Primary endpoint was change in VL at day 14. The 5-mg dose was discontinued early following recommendation from the Study Monitoring Committee and the study was unblinded following reports of five malignancies. Data for blinded study period are presented; open-label follow-up continues. *RESULTS:* One hundred eighteen patients were randomized (8% women; 34% non-whites) with median VL 36,380 (4.56 $\log_{10}$) copies/mL and CD4 count 146 cells/uL. HIV-1 RNA decrease was greater in each vicriviroc group than placebo at day 14 and week 24 ($P < 0.01$) and not different between vicriviroc groups ($P > 0.05$) (intent-to-treat [ITT]). Grade 3/4 adverse events were similar across groups. Among vicriviroc patients, two developed Hodgkin´s disease (HD) (one with prior HD); two non-Hodgkin´s lymphoma (one with prior HD); and one gastric adenocarcinoma. *CONCLUSIONS:* In treatment-experienced patients, vicriviroc demonstrated potent 14-day virologic suppression and, following optimization of background antiretrovirals, sustained antiretroviral activity over 24 weeks. The relationship of vicriviroc to malignancy is uncertain.

Prevention

Abstract TUAC0501: Herpes simplex virus type 2 (HSV-2) suppressive therapy to reduce genital and plasma HIV-1 RNA: Overview of ANRS 1285 trials, potential mechanisms and future interventions

Mayaud P, Ouedraogo A, Nagot N, et al, and the ANRS 1285 Study Group.

BACKGROUND: There is strong biological and epidemiological evidence linking HSV-2 to HIV transmission, but absence of rigorous intervention data to prove this hypothesis. *METHODS:* We conducted two proof-of-concept randomized placebo-controlled trials measuring the impact of valacyclovir (1 g daily for three months) on plasma and genital HIV-1 RNA among HSV/HIV-infected women taking highly active antiretroviral therapy (HAART) (ANRS 1285b), or not needing HAART (ANRS 1285a), in Burkina Faso. We discuss results of both trials, which have been reported separately, and mechanisms underlying the findings. *RESULTS:* The ANRS 1285a trial (n = 140) showed that both the frequency and quantity of genital HIV-1 RNA shedding were significantly reduced by valacyclovir, with a 20% decrease in quantity of HIV-1 RNA from one bi-weekly measurement to the next ($P < 0.01$). There was a rapid and sustained significant reduction in plasma HIV-1 RNA of 0.5 log copies/mL over three months. The ANRS 1285b (n = 60) did not show an impact of valacyclovir on genital HIV-1 RNA overall, but found a borderline-significant effect on genital HIV-1 quantity in the subgroup of women shedding HIV-1 at baseline ($P = 0.09$). There was some evidence of a reduction in plasma HIV-1 RNA ($P = 0.06$). Results of both trials suggest that effect on genital HIV-1 RNA is driven partly by concomitant reduction in plasma HIV-1 RNA, and partly by the facilitating role of HSV-2 on HIV-1 genital replication, although this effect was limited in women taking HAART. Plausible explanations for impact on plasma HIV-1 include immunological mechanisms, circulating soluble factors and/or HIV-infected cells, or effect on other herpes-related viruses. *CONCLUSIONS:* The ANRS 1285 trials are the first to demonstrate impact of HSV on HIV transmissibility *in vivo*. If confirmed by ongoing intervention trials, these findings support an important role of HSV-2 control in HIV prevention. Additionally, our data provide a rationale for interventions evaluating the impact of (val)acyclovir on HIV immunological and virological correlates.

Abstract TUAC0505: Is the occurrence of sexually transmitted infections related to seroconversion among HIV-discordant couples?

Rufagari MJ, Bekan Homawoo B, Marion-Landais S, Allen S, and the Rwanda-Zambia HIV Research Group.

BACKGROUND: Sexually transmitted infections (STIs) are known to be associated with HIV transmission. In Africa, discordant couples are among the highest risk group for HIV transmission. Effective treatment of an STI may be integral in the reduction of HIV transmission within discordant couples. *METHODS:* Using multivariate analysis, we analyzed data on 1,076 HIV-discordant couples, for whom we recorded quarterly information on male and female health status, including clinically and laboratory-diagnosed STIs (syphilis, genital ulcer disease, trichomonas, and male urethral discharge) and seroconversions. We distinguished individuals who had experienced STIs prior to seroconversion from those individuals who had not experienced an STI and did not seroconvert. *RESULTS:* Out of a cohort of 1,076, 42 individuals seroconverted (25 males, 17 females). Fifty-six percent of males and 41% of females had reported an STI prior to seroconversion. HIV-negative partners who had been infected in discordant couples were more likely to have experienced an STI, with a crude odds ratio (OR) of 3.88 (2.08 to 7.23), compared to those who did not seroconvert. They are also more likely to have reported inconsistent condom use, with a crude OR of 3.29 (1.69 to 6.40). After adjustment, the OR for an STI was 3.49 (1.86 to 6.55), and the OR for inconsistent condom use was 2.94 (1.50 to 5.77). *CONCLUSIONS:* Early diagnosis and treatment of STIs can significantly reduce HIV transmission among discordant couples. When clinically indicated, treatment can serve as an effective tool for HIV prevention, in addition to condom use and behavioral interventions. With proper education and counseling, discordant couples may be more inclined to report STI symptoms to their doctors or local health centers, thereby decreasing their risk of HIV transmission. In addition, policymakers should prioritize STI management on the public health agenda in order to make a substantial impact on HIV incidence in their communities.

Abstract TUAC0504: Anal sexually transmissible infections as risk factors for HIV seroconversion: Data from the HIM cohort

Jin F, Prestage G, Mao L, et al.

BACKGROUND: Sexually transmitted infections (STIs) are believed to increase the risk of HIV acquisition, but there are relatively few studies in homosexual men. As HIV infection is mostly transmitted in this population through receptive anal intercourse, we examined anal STIs as risk factors for HIV seroconversion. *METHODS:* Community-based strategies were used to enroll 1,427 initially HIV-negative homosexual men between 2001 and

2004 in Sydney, Australia. They were followed for a median of 2.0 person-years (PY), and 87% attended at least one follow-up visit. Men were tested annually for HIV, and for gonorrhea and chlamydia in the urethra and anus (strand displacement amplification, BDProbeTec). They were interviewed twice a year, and participants also reported diagnoses of STIs since their last interview. *RESULTS:* There were 38 HIV seroconversions, an incidence of 0.94 per 100 PY. HIV seroconversion was significantly associated with a higher number of episodes of receptive unprotected anal intercourse (UAI) with a partner of unknown HIV status (P trend < 0.001) or with a partner known to be HIV-positive (P trend < 0.001). After controlling for sexual behavior, a study diagnosis of anal gonorrhea was strongly related to HIV seroconversion (relative risk [RR] = 13.61, 95% confidence interval [CI] 3.93 to 47.14). Most cases of anal gonorrhea diagnosed were asymptomatic. Reporting anal warts was also associated with increased HIV incidence (adjusted hazard ratio [HR] = 2.85, 95% CI 1.08 to 7.52). *CONCLUSIONS:* HIV incidence in homosexual men in Sydney is about 1%. In addition to receptive UAI with HIV status-unknown or HIV-positive partners, certain anal STIs were independently associated with HIV seroconversion. Asymptomatic anal STIs may be important cofactors in HIV transmission. These findings suggest that frequent sexual health screening and prompt treatment of anal STIs may be an important means of HIV prevention in homosexual men.

Abstract TUPE0453: Life stress increases sexual risk behavior and risk for HIV infection among younger MSM: Results from the Polaris HIV Seroconversion Study

Calzavara L, Burchell A, Remis R, et al, and the Polaris Study Team.

BACKGROUND: Incidence of new HIV infections among MSM is rising or remains unacceptably high. While sexual risk behaviors are well documented, less is known about factors leading to risk behaviors. The objective is to determine whether stressful life events increase the risk of HIV infection through their intermediate effect on sexual risk behavior. *METHODS:* Data from 358 gay and bisexually identified men (124 seroconverters, 234 controls) enrolled as of December 2004 were analyzed. Documented recent seroconverters (cases) reported life stress and behavior during the period of infection (median six, range three to 27 months). HIV-negative controls were asked about an equivalent time period. Stressful life events were measured retrospectively using a 35-item checklist. Multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). *RESULTS:* Cases reported more stressful life events than controls (P = 0.0004). The odds of HIV infection were 3.14 times greater among men who reported more than five stressful events compared to men who reported none (95% CI 1.64 to 5.98). Financial- or security-related events resulted in increased risk among men aged <30 (OR = 4.42, 95% CI 1.53 to 12.7), but not among older men. Problems due to alcohol or drugs increased risk (OR = 2.02, 95% CI 1.20 to 3.42). Adjustment for receptive anal sex (RAS), the proposed intermediate variable in the causal pathway between life stress and infection, resulted in decreased ORs but did not entirely eliminate life stress effects. The RAS-adjusted OR for more than five events was 2.16 (95% CI 1.07 to 4.38). *CONCLUSIONS:* Results suggest younger men may use sexual behavior to cope with financial stressors. Life stress was related to HIV infection but there was evidence of mediation via receptive anal sex. The remaining effect of life stress may be due to other pathways (eg, increased likelihood of encountering an HIV-positive partner). Alternatively, stress may act as a biological cofactor through increased susceptibility upon exposure.

Abstract THPE0712: The relationship of methamphetamine and popper use with HIV seroconversion among MSM in the Multicenter AIDS Cohort Study

Plankey MW, Ostrow DG, Cox C, et al, and the Multicenter AIDS Cohort Study (MACS).

BACKGROUND: The association between use of methamphetamine (CM) and poppers (P) and HIV seroconversion (SC) for men who have sex with men (MSM) was examined using longitudinal data from the Multicenter AIDS Cohort Study (MACS). *METHODS:* Seronegative men (n = 4,003) at enrollment for phases I (1984 to 1991) and II (1996 to 2004), were identified when drug use questions were asked. Cumulative indices of CM and P were calculated as the proportions of follow-up visits with use of CM or P. Covariates included race/ethnicity, cohort, study center, educational level, number of sexual partners (SP), number of unprotected insertive anal sexual (UIAS) partners, number of unprotected receptive anal sexual (URAS) partners, insertive rimming, cocaine use since last visit, ecstasy use since last visit, any needle use since last visit, Center for Epidemiologic Studies Depression Scale (CESD) >16 since last visit, and alcohol consumption. A relative SC rate (CM+ versus CM-) for the combined phases was calculated using Poisson regression. Cox proportional hazards modeling with late entries and time-dependent covariates was performed for the combined phases as well as the first phase. Interaction terms CM*P, CM*URAS, and P*URAS were also tested. RESULTS: The relative SC rate (CM+ versus CM-) adjusted for age and race/ethnicity was 5.85 (95% confidence interval [CI]: 4.73 to 7.23] per person/visit for the combined phases. Unprotected receptive anal sex was the primary risk factor for SC. After adjusting for the significant covariates, CM and P demonstrated an independent relative hazard risk (HR) for SC of 1.5 and 2.5, respectively, with a joint relative hazard > 3.7. These HRs were similar for the combined phases and phase I only. None of the three interaction terms was statistically significant. *CONCLUSIONS:* There is an independent cumulative association of CM and P use on SC in the MACS. Examination of patterns of CM and P use will be necessary to elucidate effective primary and secondary prevention strategies and their impact on the therapeutic strategies of HIV-positive MSM.

Abstract THLB0103: Findings from a double-blind, randomized, placebo-controlled trial of tenofovir disoproxil fumarate (TDF) for prevention of HIV infection in women

Peterson L, Taylor D, Clarke EEK, et al.

BACKGROUND: Animal studies have suggested that TDF may be effective for prophylaxis against HIV infection. We investigated the safety and preliminary prophylactic effectiveness of a daily dose of 300 mg TDF versus placebo in HIV-uninfected women. *METHODS:* Between June 2004 and March 2005, we enrolled 936 HIV-negative women into a double-blind, randomized trial (1:1 TDF:placebo) in Ghana, Cameroon, and Nigeria. Participants made up to 12 monthly visits for study drug re-supply, HIV testing and adverse event (AE) reporting. Laboratory testing (serum creatinine, phosphorus, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) was done quarterly, and ALT/AST levels were monitored in a subset of participants after study drug was withdrawn. Analysis of laboratory abnormalities was restricted to data from Ghana and Cameroon. *RESULTS:* The most common AEs were malaria, candidiasis, headache, abdominal pain, and dizziness, with no significant differences between treatment groups. Furthermore, no significant differences emerged between groups for grade 3 or higher laboratory abnormalities. Specifically, none of the 363 participants in the TDF group had ALT or AST elevations greater than 170 U/L prior to product withdrawal, and two and three of the 368 participants in the placebo group had elevated (>170 U/L) ALT and AST levels, respectively. Two participants in the TDF group and one in the placebo group had decreases in phosphorus to less than 1.5 mg/dL. One participant in the placebo group had a creatinine elevation greater than 3.0 mg/dL. Two HIV infections were diagnosed in participants randomized to TDF (rate = 0.86 per 100 person-years) and six in participants receiving placebo (rate = 2.48 per 100 person-years), yielding a rate ratio of 0.35 (95% confidence interval 0.03 to 1.93). *CONCLUSIONS:* Tenofovir did not increase the rate of adverse events or grade 3 or 4 laboratory abnormalities in participants during or after use. The number of HIV infections was insufficient to conclude that TDF protected against HIV infection.

HIV Drug Resistance

Abstract WEAB0104: Maternal immune response and clinical outcomes on NNRTI-based antiretroviral therapy (ART) following exposure to single-dose nevirapine (NVP) for prevention of mother-to-child HIV transmission (PMTCT)

Chi B, Sinkala M, Levy J, et al.

BACKGROUND: Single-dose mother-infant NVP is widely used for PMTCT, but enthusiasm for it has waned over concerns of antiretroviral drug resistance in exposed mothers. *METHODS:* We studied women under HIV care in Lusaka, Zambia, where both ART and NVP-based PMTCT are widely available. Antiretroviral therapy is initiated according to WHO guidelines; first-line regimens are NNRTI-based. We defined treatment failure as suboptimal CD4 response (<50 cells/uL increase at six months, >30% decline from peak, or return to baseline), worsening WHO stage, or death. *RESULTS:* From May 2004 to November 2005, 4,552 women initiating NNRTI-containing ART had data regarding peripartum NVP exposure. Four hundred forty-five (10%) had previously used NVP for PMTCT. Median time from NVP ingestion to ART initiation was 502 days (range: nine to 1,701); 271 (81%) were exposed >180 days prior. Mean baseline CD4 count was higher in the NVP-exposed group compared to those without exposure (177 versus 146 cells/uL; P < 0.0001). However, mean CD4 change from baseline did not differ at six (+150 versus +145 cells/uL; P = 0.69) or 12 months (+184 versus +181 cells/uL; P = 0.94). Findings remained after adjustments for age, WHO stage, baseline CD4 count, and recent tuberculosis. Among women reporting NVP use, mean six-month CD4 change was similar among women with recent (<6 months) versus remote (> 6 months) exposure (+161 versus +147 cells/uL; P = 0.73). Overall, 18% failed treatment, but there was no difference based on NVP exposure in multivariable analysis (adjusted hazard ratio [AHR] = 1.2; 95% confidence interval

[CI] = 0.9 to 1.5). When compared to non-exposed individuals, women with recent (AHR = 1.5; 95% CI = 0.9 to 2.6) and remote (AHR = 1.1; 95% CI = 0.8 to 1.5) NVP exposure appeared to have similar risks for treatment failure. *CONCLUSIONS:* In this large programmatic ART cohort in Zambia, exposure to NVP for PMTCT was not associated with attenuated maternal immune response or worse clinical outcomes overall. Further studies are needed to determine the potential impact on treatment failure of timing between NVP exposure and ART initiation, particularly among women reporting recent NVP use.

Non-Occupational Post-Exposure Prophylaxis

Abstract TUPE0434: Previous use of non-occupational post-exposure prophylaxis against HIV (NPEP) and subsequent HIV infection in homosexual men: Data from the HIM cohort

Grulich A, Jin FY, Prestage G, et al.

BACKGROUND: Non-occupational post-exposure prophylaxis (NPEP) is increasingly being used to prevent HIV. In Sydney, guidelines recommending NPEP have been in place since 1998, and community awareness of availability is high. We examined the relationship between previous use of NPEP and future HIV infection in a cohort of homosexual men. *METHODS:* Community-based strategies were used to enroll 1,427 initially HIV-negative homosexual men between 2001 and 2004 in Sydney, Australia. They were followed up for a median of 2.0 person-years (PY), and 87% attended at least one follow-up visit. At each annual interview, men reported whether they had used NPEP and were serologically tested for HIV. *RESULTS:* There were 38 HIV seroconversions, giving an incidence of 0.94 per 100 PY. At baseline, 79% of men had heard of NPEP, and 6% of men had received it. By the fourth study interview, 95% of participants had heard of NPEP. Each year, between 2% and 3% of participants reported receiving NPEP. Of the men who had completed four study interviews, 13% had received NPEP. These men reported more non-concordant unprotected anal intercourse (NC-UAI) than those who had not received NPEP ($P < 0.001$). Men who had received NPEP at baseline continued to be at high risk. They were more likely than those who did not receive NPEP to report NC-UAI one year later (50% and 36%, $P = 0.009$). Men who had previously received NPEP continued to be at increased risk of HIV in the future (incidence of 2.37 per 100 PYs, relative risk [RR] 2.30, 95% confidence interval [CI] 1.05 to 5.06). *CONCLUSIONS:* Non-occupational post-exposure prophylaxis use is relatively frequent in homosexual men in Australia. Those who have previously received NPEP continue to report high levels of risk behavior and have higher rates of HIV infection. These findings highlight the need for further HIV prevention interventions targeted to homosexual men who receive NPEP.

Abstract TUPE0432: Tenofovir-based regimens for non-occupational post-exposure prophylaxis (NPEP): Improved tolerability and adherence compared to ZDV-based regimens

Mayer K, Mimiaga M, Cohen D, et al.

BACKGROUND: Fenway Community Health began providing NPEP in 1997. Concerns about suboptimal tolerability and completion rates with zidovudine (ZDV)-containing regimens led to the development of phase 4 studies of tenofovir DF (TDF) and lamivudine (3TC), and subsequently, TDF/emtricitabine (FTC), for NPEP. *METHODS:* Starting in March 2005, participants who presented after high-risk exposures were offered once-daily TDF (300 mg)/FTC (200 mg) for 28 days. The clinical experience of participants who took TDF/FTC was compared to historical controls who had taken TDF/3TC ($n = 57$), ZDV/3TC ($n = 140$), or ZDV/3TC and a third drug ($n = 143$) for NPEP. *RESULTS:* Two of the 37 participants who initiated NPEP and TDF/FTC withdrew from the study after their sources were found to be HIV-uninfected, and one was withdrawn because of hepatitis B infection. Ninety-seven percent of TDF/FTC participants were male and 86% were men who have sex with men (MSM), with a mean age of 35 years. Tenofovir/emtricitabine participants were demographically similar to historical controls. The four-week follow-up rates were 88.2% for TDF/FTC; 96.6% for TDF/3TC; 44.9% for ZDV/3TC; and 48.3% for the ZDV/3TC/one other drug group ($P < 0.001$). Tenofovir/emtricitabine users were more likely to complete their regimens as prescribed compared to those who were given ZDV-containing regimens ($P < 0.001$). Tenofovir/emtricitabine users more often reported diarrhea than those who used TDF/3TC ($P = 0.03$) or a ZDV-containing regimen ($P = 0.04$), and were more likely to report dizziness/lightheadedness ($P = 0.02$). However, TDF/FTC users reported fatigue less often than those who used any ZDV-containing regimen ($P = 0.02$), reported abdominal pain less often than those who used TDF/3TC ($P = 0.04$), and reported nausea/vomiting less often than those who used a ZDV-containing regimen ($P = 0.02$). No acute HIV infections have been detected among participants who used TDF-based regimens. *CONCLUSIONS:* Tenofovir/emtricitabine is well-tolerated for NPEP, with higher completion rates than ZDV/3TC-containing regimens. Better-tolerated qd regimens for NPEP may improve adherence and minimize loss to follow-up.

HIV Testing

Abstract MOPE0517: HIV prevalence and undiagnosed infection among community samples of gay men in the United Kingdom: Five-city comparison

Williamson L, Dodds J, Mercey D, Johnson A, Hart G.

BACKGROUND: Gay men remain the group most at risk of HIV in the UK, and the number of diagnoses among them has increased in recent years. Here, we examine HIV prevalence and undiagnosed infection among community samples of gay men in five UK cities. *METHODS:* Cross-sectional surveys were conducted in gay commercial venues in London, Brighton, and Manchester in 2003/2004, and Glasgow and Edinburgh in 2005. In total, 4,384 men completed questionnaires and 3,661 provided oral fluid samples, using Orasure™ kits, to be tested anonymously for HIV (oral fluid sample response rates were: London, 62.9%; Brighton, 66.8%; Manchester, 70.4%; Glasgow, 48.4%; and Edinburgh, 54.8%). *RESULTS:* HIV prevalence was 12.3% in London (95% confidence interval [CI] 10.7% to 14.1%), 13.7% in Brighton (95% CI 10.6% to 17.5%), 8.6% in Manchester (95% CI 6.1% to 12.0%), 3.6% in Glasgow (95% CI 2.5% to 5.2%) and 5.5% (95% CI 3.9% to 7.6%) in Edinburgh ($P < 0.01$). HIV-positive men were more likely than HIV-negative men to report unprotected anal intercourse (UAI) with multiple partners (34.8% versus 16.1%, $P < 0.01$), UAI with casual partners (37.2% versus 22.2%, $P < 0.01$), UAI with partners of unknown or discordant HIV status (32.3% versus 25.0%, $P < 0.05$), and sexually transmitted infections in the previous year (39.1% versus 16.8%, $P < 0.01$). Of the HIV-positive men, 41.2% were undiagnosed (London, 44.1%; Brighton, 33.3%; Manchester, 36.7%; Glasgow, 48.1%; and Edinburgh, 36.4%). Over half of this group (70 men, 53.4%) reported that the result of their most recent HIV test was negative and that they currently perceived themselves to be negative. *CONCLUSIONS:* This is the first study to compare HIV prevalence in community samples of gay men across the UK. There was substantial HIV prevalence in all five cities and, given the high level of sexual risk behavior, undiagnosed infection, and incorrect assumptions of status, the potential for HIV transmission is of concern and requires targeted prevention efforts.

Adherence

Abstract THPE0729: Daily living, functional health, and adherence to antiviral drug regimens in young adult, HIV-positive methamphetamine users

Carroll R.

BACKGROUND: In areas across North America and Europe, methamphetamine use has been associated with HIV transmission. Moreover, many living with HIV and in treatment are methamphetamine users. When methamphetamine use interferes with adherence to ARV treatment regimens, individuals become vulnerable to the development of resistant viral strains, threatening both individual health and the public health. The purpose of this study was to describe daily living and its relationship to the maintenance of functional health in HIV-positive young adults on highly active antiretroviral therapy (HAART) who have recently used methamphetamines, with or without "party drugs." This study is significant because it describes the intersection of methamphetamine use and HIV treatment in young adults, expanding on current research by focusing on daily living and functional health management. *METHODS:* Ethnographic methodology guided the research plan, and audiotaped/transcribed semi-structured interviews were the means of data collection. The interview was theoretically grounded in the Carnevale Nursing Theory of Health Management, which focuses on explicating the resources and requirements employed and required by individuals in their daily health maintenance processes. Results were analyzed using a constant comparison approach to qualitative data management. *RESULTS:* Among the specific themes identified in the study were: 1) the association between survival, sex, and methamphetamine use; 2) difficulties in accessing health care resources, which influenced the use of methamphetamine; and 3) lack of assessment by health care providers for methamphetamine use, and/or lack of knowledge related to health promotion in ARV-taking methamphetamine users. *CONCLUSIONS:* This descriptive study focused on the ways by which requirements of daily living are balanced against individual and environmental resources available to the participants. This study found that while methamphetamine use may challenge adherence to medical treatment, there are specific systemic sociocultural and health care environment interventions which could better support the health promotion and maintenance of young adult HIV-positive methamphetamine users.

Prevention of Mother-to-Child Transmission of HIV

Abstract THAC0101: 18-month effectiveness of short-course perinatal antiretroviral regimens combined to infant-feeding interventions for PMTCT in Abidjan, Côte d'Ivoire. DITRAME PLUS ANRS 1201/1202 2001-2005

Leroy V, Ekouévi DK, Dequae-Merchadou L, et al, and the DITRAME PLUS ANRS 1201/1202 Study Group.

BACKGROUND: We assessed the 18-month effectiveness of two short-course antiretroviral regimens combined with infant-feeding options offered subsequently for PMTCT of HIV-1 in Abidjan, Côte d'Ivoire. *METHODS:* Any HIV-1-infected pregnant woman, age ≥ 18, who received a perinatal PMTCT antiretroviral prophylaxis ≥32 to 36 weeks of gestation (zidovudine [ZDV] ± lamivudine [3TC] + single-dose nevirapine [sdNVP]) was eligible if she gave a live birth. Two infant-feeding interventions were systematically proposed prenatally: formula-feeding (free of charge), or exclusive breastfeeding with early cessation from four months. Blood samples for HIV diagnosis were taken at day two, week four to six, month three, then every three months until 18 months, or two months after stopping breastfeeding, if any. Pediatric HIV infection was defined as a positive polymerase chain reaction (PCR) at any age, or if aged >18 months, a positive HIV serology. Postnatal transmission (PT) was defined as a child with a negative HIV-1 PCR from a sample obtained at age >30 days who later became infected, or peripartum infection. Cumulative transmission risks (CRs) of infection were estimated using the Turnbull method in each infant-feeding group, defined at day two. *RESULTS:* Between March 6, 2001, and July 31, 2003, 711 live-born children were enrolled, of whom 24 were excluded: 22 HIV-indeterminate (3%), and two not classified for infant-feeding modalities. At 18 months, 60 children were HIV-infected, of whom 12 (20%) were PT (one in the formula-fed group): CRs were 0.17 (95% confidence interval [CI]: 0.099 to 0.307) in the 168 ZDV + sdNVP breastfed group; 0.09 (95% CI: 0.057 to 0.136) in the 195 ZDV + sdNVP formula-fed group; 0.068 (95% CI: 0.0358 to 0.105) in the 198 ZDV + 3TC + sdNVP breastfed group, and 0.053 (95% CI: unavailable) in the 126 ZDV + 3TC + sdNVP formula-fed group. Overall, low maternal CD4 count (<500 cells/mm^3) and ZDV + sdNVP regimen (reference: ZDV + 3TC + sdNVP) were both significantly associated with long-term infection, while having ever been breastfed was not a determinant. *CONCLUSIONS:* A combination of perinatal ZDV + 3TC + sdNVP associated with infant feeding interventions reduces significantly MTCT of HIV with long-term benefit until age 18 months.

Initiation of Antiretroviral Therapy

Abstract THLB0201: A two-year randomized controlled clinical trial in antiretroviral-naive subjects using lopinavir/ritonavir (LPV/r) monotherapy after initial induction treatment, compared to an efavirenz (EFV) three-drug regimen (Study M03-613)

Cameron W, da Silva B, Arribas J, et al.

BACKGROUND: With robust pharmacokinetics, high potency, and high genetic barrier to resistance, LPV/r is a good candidate for evaluation as monotherapy for HIV infection. *METHODS:* One hundred fifty-five antiretroviral-naive HIV-1-positive subjects were randomized 2:1 to LPV/r + zidovudine (ZDV) + lamivudine (3TC) induction (n = 104) for at least 24 weeks followed by maintenance LPV/r monotherapy after three consecutive monthly viral loads (VLs) <50 copies/mL, or to EFV + ZDV + 3TC (n = 51). The primary endpoint was the proportion achieving and maintaining VL <50 copies/mL through 96 weeks. *RESULTS:* Baseline characteristics were similar between arms. Ninety-two (88%) of 104 LPV/r subjects started monotherapy. Seventy-nine LPV/r (69/92 on monotherapy) and 34 EFV-treated subjects completed the study. Drug-related discontinuations occurred in 3% of LPV/r-treated and 2% of EFV-treated subjects. In the primary analysis, 50% of LPV/r-treated and 61% of EFV-treated subjects achieved and maintained VL <50 copies/mL through 96 weeks (intent-to-treat, previous failure = failure, P = 0.23). By Kaplan-Meier analysis, the proportions maintaining VL <50 and <500 copies/mL through 72 weeks on LPV/r after deintensification were 62% and 84% respectively. Corresponding Kaplan-Meier estimates for EFV subjects after three consecutive VLs <50 copies/mL were 91% <50 (P = 0.002 versus LPV/r monotherapy) and 95% <500 copies/mL (P = 0.10 versus LPV/r monotherapy). Lopinavir/ritonavir monotherapy subjects with VL rebound to 50 to 500 copies/mL generally demonstrated viral resuppression to <50 copies/mL while continuing LPV/r monotherapy (11/12) or with resumption of nucleoside reverse transcriptase inhibitors (NRTIs) (two of four). New protease inhibitor (PI) resistance mutations were detected in two of 15 (13%) LPV/r-treated subjects, while non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations were detected in one of five (20%) EFV-treated subjects (P > 0.9). *CONCLUSIONS:* After successful induction treatment with LPV/r + ZDV + 3TC, LPV/r monotherapy continuously maintained VL suppression in a majority of subjects. Lopinavir/ritonavir monotherapy had more intermittent VL increases between 50 and 500 copies/mL versus EFV + ZDV + 3TC, but most subjects returned to <50 copies/mL. Lopinavir/ritonavir monotherapy may be effective in selected patients.

Abstract THLB0204: A prospective, randomized, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection—ACTG 5142

Riddler SA, Haubrich R, DiRienzo G, et al, and the AIDS Clinical Trials Group 5142 Study Team.

BACKGROUND: First-line therapy with two nucleoside reverse transcriptase inhibitors (2NRTI) and either efavirenz (EFV) or lopinavir/ritonavir (LPV/r) has not been compared in a randomized trial; and the NRTI-sparing combination of LPV/r + EFV has not been studied as initial therapy. *METHODS:* Randomized, open-label, prospective trial comparing three class-sparing regimens for naive subjects: LPV + EFV (L/E) versus LPV/r + 2NRTI (LPV; soft-gel bid) versus EFV + 2NRTI (EFV). Nucleoside reverse transcriptase inhibitors were selected before randomization from zidovudine (ZDV), stavudine (d4T XR), or tenofovir (TDF) (each plus lamivudine [3TC]). Primary objectives were to compare between arms the time to confirmed virologic failure (VF; HIV-1 RNA >200 after week 32) and regimen completion (RC; VF or toxicity-related discontinuation of any regimen component). The significance level adjusted for multiple between-arm comparisons and interim analyses was 0.016. Analyses were intent-to-treat (ITT) (censored data not equal to failure). *RESULTS:* Seven hundred fifty-three enrolled subjects (median CD4 count: 182 cells/mm^3, median HIV-1 RNA: 100,000 copies/mL) were followed for a median 112 weeks. Nucleoside reverse transcriptase inhibitor choice was ZDV 42%, d4T XR 24%, and TDF 34%. No statistically significant between-arm differences were observed in time to VF or RC (P > 0.016). However, there was a trend toward shorter time to VF (P = 0.033) and RC (P = 0.065) for LPV compared with EFV. Kaplan-Meier estimates of the proportions without VF by week 96 were 73%, 67%, and 75% for L/E, LPV, and EFV arms, respectively. At week 96, the percentages with HIV-1 RNA <50 copies/mL were 83%, 77%, and 89% for the L/E, LPV, and EFV arms, respectively (P = 0.003 LPV versus EFV). The median 96-week increase in CD4 count was significantly greater for LPV-containing arms (L/E +268 cells/mm^3, LPV +285 cells/mm^3) than for EFV (+239.5; P = 0.01). The time to treatment-limiting toxicity was similar for all arms. *CONCLUSIONS:* Compared with a regimen of EFV + 2NRTI, LPV/r + 2NRTI tended to have shorter time to virologic failure and regimen completion. The NRTI-sparing regimen of LPV/r + EFV had similar efficacy and safety to EFV + 2NRTI.

Abstract THLB0202: MONARK trial (MONotherapy AntiRetroviral Kaletra): 48-week analysis of lopinavir/ritonavir (LPV/r) monotherapy compared to LPV/r + zidovudine/lamivudine (ZDV/3TC) in antiretroviral-naive patients

Delfraissy J-F, Flandre P, Delaugerre C, et al.

BACKGROUND: Guidelines for the use of antiretroviral drugs for HIV-1 infection recommend combining three agents. However, toxicities, cost, and complexity of such regimens warrant the search for other options. *METHODS:* MONARK is a pilot, prospective, open-label, randomized, 96-week trial comparing the safety and efficacy of LPV/r monotherapy to a standard LPV/r + ZDV/3TC regimen. Antiretroviral-naive subjects without baseline resistance to study drugs, with viral load (VL) 100,000 copies/mL, and CD4 count 100 cells/mm^3 were randomized to either LPV/r or LPV/r + ZDV/3TC. The primary endpoint was VL <400 copies/mL at week 24 and <50 copies/mL at week 48. Sub-optimal virologic response was defined as (1) <1 log VL decrease by week four, (2) VL >400 copies/mL by week 24, (3) VL rebound after VL <400 copies/mL, confirmed in a second specimen. RESULTS: One hundred thirty-six subjects were randomized (83 LPV/r; 53 LPV/r + ZDV/3TC). Baseline characteristics were similar: VL (median 4.5 log LPV/r; 4.3 log LPV/r + ZDV/3TC), CD4 (median 235 cells LPV/r; 224 LPV/r + ZDV/3TC). Discontinuations through week 48 were 19% for LPV/r arm and 30% for LPV/r + ZDV/3TC arm (P = 0.03, P = 0.02). Sub-optimal virologic response occurred in nine (11%) taking LPV/r and seven (13%) taking LPV/r + ZDV/3TC. At week 48, median CD4 increase from baseline was 152 cells/mm^3 for LPV/r, 159 for LPV/r + ZDV/3TC. Through week 48, two of 83 (2%) subjects on LPV/r monotherapy developed resistance mutations (both in protease), versus one of 53 (2%) on LPV/r + ZDV/3TC (M184V). Similar tolerance was observed. *CONCLUSIONS:* Initiating antiretroviral therapy with LPV/r monotherapy demonstrated sustained virological efficacy. However, LPV/r monotherapy was associated with more episodes of viremia compared with three-drug therapy.

HIV/HCV coinfection exacerbates ESLD risk

Liz Highleyman

Patients coinfected with HIV and hepatitis C virus (HCV) are more likely to develop end-stage liver disease (ESLD) compared to patients who are HCV-monoinfected, according to a study presented by French researchers at the XVI International AIDS Conference held August 13-18, 2006, in Toronto. However, the researchers found that HIV/HCV-coinfected patients who achieved a sustained virological response to hepatitis C therapy were no more likely to progress to ESLD than their HCV-monoinfected peers.

Most studies show that coinfected patients experience more rapid liver fibrosis progression than those who are HCV-monoinfected, although this may be less likely if HIV is well-controlled. Coinfected patients are also less likely to respond to interferon (IFN)-based therapy.

Firouzé Bani-Sadr (INSERM, Paris) presented data from a study of liver disease progression among HIV/HCV-coinfected patients in France. The researchers prospectively followed 248 HIV/HCV-coinfected patients who received pegylated interferon (PEG-IFN) or conventional IFN, both with ribavirin (RBV), for 48 weeks in the RIBAVIC trial. Overall, 29% achieved sustained virological response, or continued undetectable hepatitis C viral load, 24 weeks after the completion of therapy.

The average age of the patients was 42 years, 75% were men, and 59% had hard-to-treat hepatitis C genotypes 1 or 4. Most (81%) were taking antiretroviral therapy for HIV, about half had HIV viral loads below 200 copies/mL, and the average CD4 count was 567 cells/mm^3. At the start of the study, 35% already had severe liver fibrosis or cirrhosis.

After an average follow-up period of 33 months, 17 events indicative of ESLD occurred in nine patients (4%). These events included liver decompensation (with symptoms such as severely elevated bilirubin, ascites, hepatic encephalopathy, or bleeding esophageal varices), hepatocellular carcinoma, need for liver transplant, and liver-related death. Six patients died of liver-related causes and two of other causes.

All cases of ESLD occurred in patients who did not achieve sustained virological response to anti-hepatitis C therapy, and all but one occurred in patients who had advanced fibrosis at the start of the study. End-stage liver disease did not occur in patients with severe fibrosis who permanently cleared HCV with treatment. Among non-responders, ESLD was more common among patients with advanced fibrosis who also had lower CD4 counts.

In a stratified analysis, the only independent risk factors for ESLD were cirrhosis or severe fibrosis at the start of the study ($P < 0.001$), having a CD4 count below 350 cells/mm^3 ($P = 0.022$), and lack of sustained virological response to anti-hepatitis C therapy ($P = 0.068$).

In conclusion, the researchers stated, "Our study confirms that the rate of spontaneous hepatic decompensation in coinfected patients with asymptomatic cirrhosis is higher (7.4% per year) than in [HCV]-monoinfected patients (3% to 4% per year)." The researchers further recommended that "clinicians should consider the evidence that sustained virological response seems associated with a reduction in long-term morbidity and mortality related to hepatitis C" when discussing treatment options with patients. ■

Reference

Carrat F, Cacoub P, Pol S, *et al*. Three years assessment of the risk of end-stage liver disease in HIV/HCV-coinfected patients treated for a chronic HCV infection. XVI International AIDS Conference. August 13-18, 2006. Toronto. [Abstract TUAB0301]

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Eric Hefer

For more than three years the *IAPAC Monthly* has featured members of the International Association of Physicians in AIDS Care (IAPAC), who are asked to bare their souls by answering a series of questions similar in nature to those asked in the famous *Proust Questionnaire*.

This month, *IAPAC Monthly* is proud to feature Eric Hefer, Medical Director of Calibre Clinical Consultants in Johannesburg, South Africa.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
Don Quixote charging the Rock of Gibraltar.

What activities, avocations, or hobbies interest you? Do you have a hidden talent?
My hobbies are cooking and traveling. I can make a fine venison stew, and am always ready for a barbeque!

If you could live anywhere in the world, where would it be?
In the winter I would live in Johannesburg, and in the summer I would live in Rio de Janeiro.

Who are your mentors or real life heroes?
Barney Hurwitz, Adriaan Jacobsz, and Jan van der Merwe.

With what historical figure do you most identify?
I most identify with Winston Churchill.

Who are your favorite authors, painters, and/or composers?
My favorite author is Tom Sharpe.

If you could have chosen to live during any time period in human history, which would it be?
I would choose to live during the 20 years prior to the French Revolution; otherwise, during the Roman Empire—as royalty in both cases.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
I would have become an information technology specialist—I loved playing with computers in those early days.

In your opinion, what are the greatest achievements and failures of humanity?
The greatest achievement is learning to speak, followed by the greatest failure, which is allowing lawyers to learn as well.

What is your prediction as to the future of our planet one full decade from present day?
I predict there will be an energy shortage; also, conflicts along religious lines. ■

SAY ANYTHING

The XVI International AIDS Conference, held August 13-18, 2006, in Toronto, attracted more than 24,000 delegates from around the world under the banner theme, "Time to Deliver." Following are select quotes from presentations delivered at this biannual conclave meant to provide a forum for the presentation of and discussion about clinical and social aspects of the AIDS pandemic—this year marking its 25th anniversary.

[E]nding AIDS will not be the success of one great scientist, one great community, or one great leader; it will be an accomplishment of the whole human family working together for one another.

Melinda Gates, Co-Chair of the Bill & Melinda Gates Foundation, delivering a joint keynote address, at the opening of the Conference. Her husband and fellow Co-Chair, Bill Gates, called for increased focus on HIV prevention as well as a concentrated effort on further reducing the cost of antiretroviral drugs, including generic versions.

No one has the capacity to manage HIV/AIDS alone. Universal access demands a universal response. Think of this as a borderless society for health; one that includes everyone in the continuum of HIV/AIDS prevention, treatment, care, and support; that embraces all who can make a difference, from political leaders to scientists, health workers to young people, people living with HIV, the poor, sex workers, injecting drug users, men who have sex with men, people in prison. This includes [non-governmental organizations], civil society, activists, private providers, pharmaceutical companies, community groups. And of course, this includes not only health care workers, but also the education, infrastructure, finance, and other sectors. We need a strong gender perspective in our work to ensure that women and men, girls and boys are provided with equal opportunities. All of us are responsible for the next steps as we are going back to our homes.

Anders Nordstrom, Acting Director-General, World Health Organization, at the closing session, "Time to Deliver."

People like myself who study HIV/AIDS feel their hearts sinking when we hear of trade talks collapsing. People need to understand that [such events] will impact the epidemic in the future.

Alan Whiteside, Director of the Health Economics and HIV/AIDS Research Division (HEARD), at the University of KwaZulu-Natal, South Africa, quoted in the August 14, 2006, issue of the Daily Voice, *the daily newspaper covering the Conference.*

If our generation does not recognize and act on the fact that we are sisters and brothers with responsibility to one another, we risk having our very human identity slip between our fingers.

Sister Patricia Talone, Vice President for Mission Services, Catholic Health Association, at "Faith in Action—Keeping the Promise," an ecumenical and interfaith preconference session held August 10-11, 2006, prior to the Conference. Sister Talone warned against "mean-spiritedness" against people living with HIV/AIDS.

Colonization, displacement of land, loss of culture, poor living conditions—these are issues that have a significant impact on these groups everywhere. These are not huge populations so their physical, mental, and spiritual well-being is more at risk. AIDS is just another disease that is having a disproportionate impact on these populations.

LaVerne Monette, Executive Director of Ontario Aboriginal HIV/AIDS Strategy, at the International Indigenous Peoples' satellite session, co-hosted August 11-12, 2006, by the Ontario Aboriginal HIV/AIDS Strategy and the Two-Spirited People.

Above all, we need policy makers to start fearing HIV/AIDS more than [they fear] giving rights to women.

Nafis Sadiq, United Nations Special Envoy for HIV/AIDS in Asia, at the "Women at the Frontline in the AIDS Response" session, held August 14, 2006.

PrEP is an exciting prospect for us. But the real challenge of PrEP will be in its implementation. If it works, who will get it? How will we ensure governments, study sponsors, donors, and the community work together to benefit not only the trial participants but everyone in the community?

Nimit Tien Udom, Director of the AIDS Access Foundation in Thailand, at the session entitled "What if PrEP Works?" held August 13, 2006.

Denial kills, inappropriate policies kill and excuses for not treating injecting drug users (IDUs) kill, as well.

Michel Kazatchkine, French Ambassador on HIV/AIDS and Transmissible Diseases, at an August 14, 2006, satellite session on HIV treatment for IDUs.

These treatments are blind to race and color. They work everywhere…And they especially work better when they are free.

Julio SG Montaner, Director of the British Columbia Centre for Excellence in HIV/AIDS and Director of the Canadian HIV Trials Network, at the Wednesday, August 16, 2006, session entitled "Advancing Treatment and Universal Access: A Report on State-of-the-Art and Progress."

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