

The AMERICAN ACADEMY of HIV MEDICINE

# HIV SPECIALIST

PATIENT CARE, PRACTICE MANAGEMENT & PROFESSIONAL  
DEVELOPMENT INFORMATION for HIV CARE PROVIDERS

Fall 2010

[www.aahivm.org](http://www.aahivm.org)

Caring for the *Total Patient*

## The HIV Team

Implementing  
ICD-10

4

Fighting  
Fraud

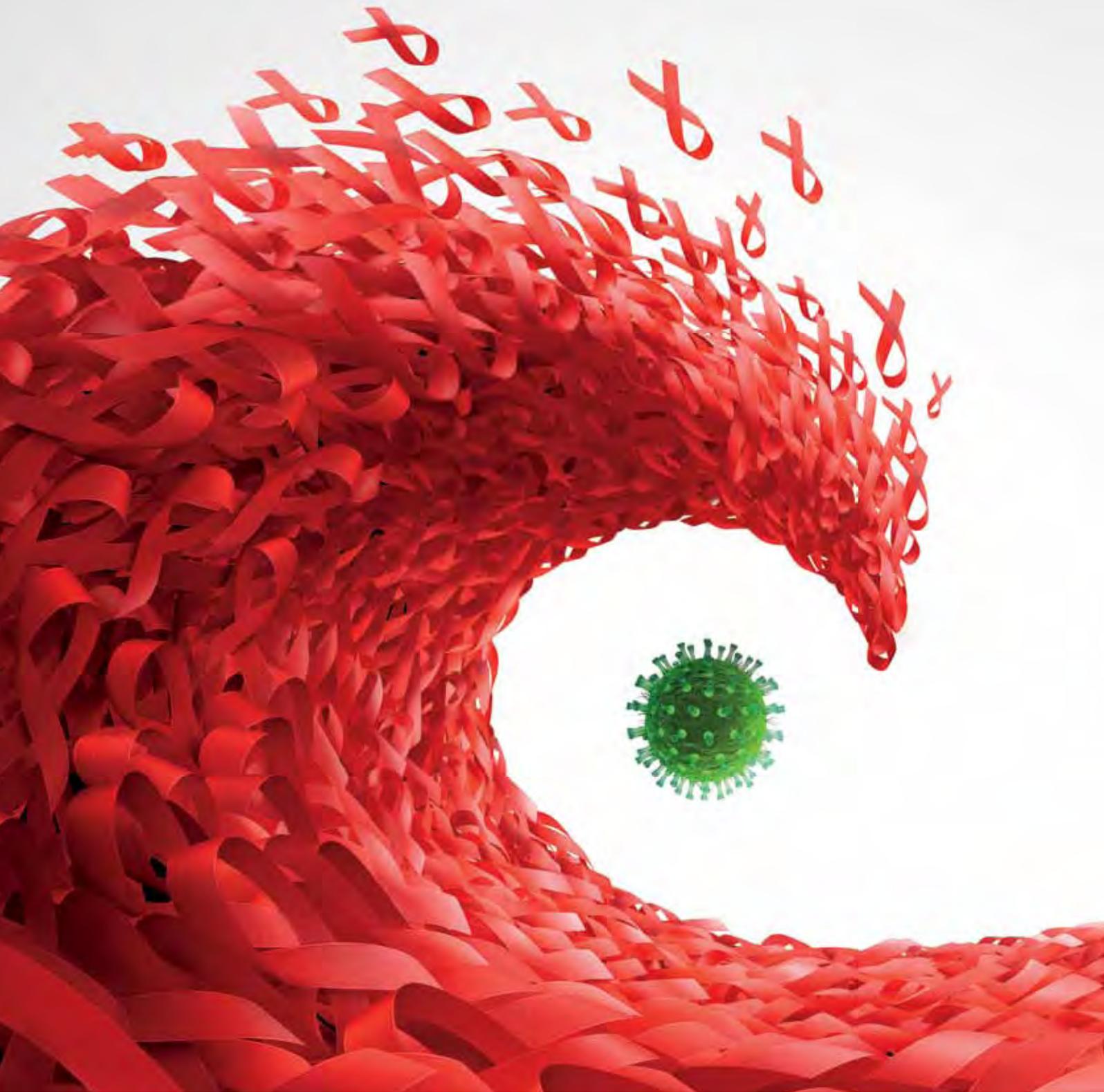
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**References:** 1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2009. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed December 1, 2009. 2. Kitahata MM, Gange SJ, Abraham AG, et al; for NA-ACCORD Investigators. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826. 3. Moore RD, Keruly JC. CD4<sup>+</sup> cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446. 4. Emery S, Neuhaus JA, Phillips AN, et al; for Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Major clinical outcomes in antiretroviral therapy (ART)-naïve participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis*. 2008;197(8):1133-1144.

# A surge of evidence supports treating HIV earlier

- **DHHS guidelines<sup>1</sup>:**

- HAART is recommended for patients with a CD4 cell count of 350–500 cells/mm<sup>3</sup>
- Half of the Panel favors initiating HAART for patients with a CD4 cell count >500 cells/mm<sup>3</sup>, while the remainder views HAART as an option
- As part of the consideration for earlier initiation of HAART, the Panel cites both the benefits and potential limitations

- **Significant improvement in patient survival<sup>2\*</sup>**

- **Better long-term CD4 cell count<sup>3†</sup>**

- **Significant reduction in the probability of morbidity<sup>4‡</sup>**

- **Lower probability of HIV transmission<sup>1</sup>**

► **Talk to your patients and help them understand the potential of earlier initiation of HAART.**



DHHS=Department of Health and Human Services.

\*69% increase in relative risk of death when treatment was deferred until CD4 cell count was  $\leq 350$  cells/mm<sup>3</sup> (versus initiating at 351–500 cells/mm<sup>3</sup>;  $P < 0.001$ ) and 94% increase in relative risk of death when treatment was deferred until CD4 cell count was  $\leq 500$  cells/mm<sup>3</sup> (versus initiating at >500 cells/mm<sup>3</sup>;  $P < 0.0001$ ), based on the NA-ACCORD analysis.<sup>2</sup>

†After 6 years, patients with a baseline CD4 cell count >350 cells/mm<sup>3</sup> achieved and maintained nearly normal CD4 levels with HAART (versus  $< 350$  cells/mm<sup>3</sup>) in an observational analysis.<sup>3</sup>

‡Earlier initiation (>350 cells/mm<sup>3</sup>) was associated with significantly reduced probability of opportunistic disease (OD), serious non-AIDS events, and non-OD deaths in an analysis of the SMART study.<sup>4</sup>



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# There Is No “I” in Team

**T**HIS PAST WEEKEND, the Washington Redskins defeated the Philadelphia Eagles by a score of 17 to 12. This is the game where Donovan McNabb, the former quarterback for the Eagles, returned to Philadelphia as the starting quarterback for the Redskins. In his remarks after the upset victory for the Redskins, McNabb described the victory as a team victory—not a personal one. As trite as that may sound, it is almost always the case.

While I am a Redskin fan and my son is a vice president with the Redskins, the real reason I start this way is because this issue of *HIV Specialist* is all about the HIV treatment team. And just as in football, successful HIV care is a team effort. We know that the medical members of the HIV care team are essential, but this issue makes the point that there are other members of the treatment team that provide essential services, including the social worker, the nutritionist, and the rest of the clinic/office staff.

The physician, and often the nurse practitioner and physician assistant, are critical in undertaking the initial diagnosis and developing a treatment regime. But as you know better than I, it is in prevention and adherence to drug therapy where other team members, such as the mental health therapist, often take a lead role. These are time consuming, iterative treatment functions that physicians often don't have enough time to manage. And even here, there can be “team extenders” like 340B pharmacies that can help in prescription management and adherence.

Four factors are likely to increase the importance, and roles of, these other team members in the coming years:

1. Due to the routine HIV testing initiative, as well as HIV patients often living a full life, the numbers of HIV/AIDS patients will continue to grow in the US.
2. The HIV patient population is increasingly poor and will need additional assistance with support services.

3. Health care reform will increase the financial access to care.
4. The AAHIVM 2009 Workforce survey and other trusted sources reflect that up to one-third of HIV practitioners will leave the field over the coming decade—and there are not nearly enough students in the pipeline to replace them.



James Friedman

So, as you read through this issue, think about how the HIV care team has changed over the past two plus decades and how it might change further in the coming years. Perhaps the “internet medical communicator” (my term) will become one of the most important new members of the HIV team—particularly in prevention and adherence—utilizing the integrated electronic medical record along with extensive electronic patient monitoring systems to implement a new era of real time medical care. I may be getting a bit ahead of myself, but just think how much HIV care has changed since the early 1980's. Our patients, our

tools and our outcomes have changed—and the mix of our teammates will continue to change as well.

As long as we are talking about the HIV care team, I would be remiss if I didn't mention the staff here at the Academy. While we all have our own areas of responsibility, we also work together to produce an integrated program. There is hardly an activity that doesn't utilize the talents of several of our staff.

We understand that by working cohesively, we will ultimately do a better job of supporting you, the HIV care provider. As the Academy enters its second decade, our team will continue to represent and advocate for your team, the work you do and the patients you treat.

By the time you read this article, the Redskins may have won or lost several more games. But you can be sure that the HIV treatment team will have improved and lengthened the lives of thousands of HIV patients.

Bet on it.

HIV

# Ready *Set* Code!



**HEALTH CARE PROVIDERS, INCLUDING THOSE WHO TREAT HIV PATIENTS,** need to prepare now for a major change in diagnosis and procedure codes if they hope to get paid for their services in the future.

*The issue is complicated, but must be faced as the U.S. health care system will change from ICD-9 to ICD-10 diagnosis and procedure codes effective October 1, 2013. Following is detailed information provided by the Centers for Medicare and Medicaid Services at the request of HIV Specialist.*

Leading up to the October 1, 2013, compliance date, providers should be aware of these important dates:

- Beginning January 2011, providers should begin testing Version 5010 transaction standards with their trading partners.
- January 1, 2012 is the date for Version 5010 compliance.

Prepare now to avoid potential reimbursement delays. If you do not use Health Insurance Portability and Accountability Act (HIPAA) Version 5010 transaction standards starting January 1, 2012, and ICD-10 codes when submitting claims with dates of service on or after October 1, 2013, your claims may not be paid.

## What's Changing? Who's Affected?

"Unlike ICD-9 codes, ICD-10 diagnosis codes are alphanumeric, have three to seven digits, and are much more descriptive", explained Tony Trenkle, director of the Office of E-Health Standards and Services at the Centers for Medicare & Medicaid Services.

"For example, in ICD-9, a diagnosis code currently used for HIV, V19.8, "family history of other conditions," is vague. In ICD-10, the diagnosis code Z83.0, now specifies 'family history of human immunodeficiency virus (HIV) disease,' which is more accurate and detailed."

ICD-10 will affect diagnosis and inpatient procedure coding for everyone covered by the HIPAA, not just those who submit Medicare claims. This change does not affect Current Procedural Terminology (CPT) coding for outpatient procedures, however.

In addition to the code set changes, standards for electronic administrative transactions (such as eligibility inquiries and remittance advices) are being updated from the current Version 4010/4010A1 to Version 5010 on January 1, 2012. Version 5010 accommodates both the ICD-9 and the ICD-10 code set structures. To allow time to meet the January 2012 implementation date, providers should

begin testing Version 5010 with their trading partners starting in January 2011.

Providers who use practice management software, a clearinghouse, third-party biller, or some other way to transmit information between themselves and a health care plan, will need to upgrade their software or work with a clearinghouse or billing service whose systems can accommodate both the Version 5010 standards and the ICD-10 code sets.

## Preparing for the Transition

Start with a gap analysis to determine the impact on your organization of both Version 5010 and ICD-10. Use that information to develop an implementation plan, with a detailed timeline, and estimate of costs. Providers should take the following steps now:

1. Check with your billing service, clearinghouse, or practice management software vendor. Your third-party biller and clearinghouse need to make sure that you will be compliant by the deadlines. Software vendors should be developing and testing products that will enable Version 5010 testing with your payers and billing services starting January 2011. Testing with ICD-10 should start sometime after Version 5010 implementation in January 2012, to allow for full ICD-10 implementation on October 1, 2013.
2. Start planning to implement the ICD-10 transition. Meet with your professional and support staff. Discuss where codes are used within your organization to help you assess impact. Assign roles and responsibilities for addressing the transition.
3. Identify needs and resources. Consider changes that might be required. Develop a budget and timeline that take into account specific workflow needs, vendor readiness, and staff knowledge and training.

## Version 5010/ICD-10 Resources

The CMS Web site, [www.cms.gov/ICD10/](http://www.cms.gov/ICD10/), has official CMS resources to help you prepare for Version 5010 and ICD-10. CMS will continue to add new tools and information to the site throughout the course of the transition. **HIV**

Prepare now  
for health care  
code transition.  
It's coming.



## ICD-10

Official CMS Industry Resource for the ICD-10 Transition  
[www.cms.gov/ICD10](http://www.cms.gov/ICD10)

### Transition Dates for Version 5010/ICD-10

- ➔ **January 2011:** Version 5010 testing starts across the health care system. Medicare begins accepting Version 5010 electronic claims.
- ➔ **January 1, 2012:** All electronic claims must be submitted using Version 5010.
- ➔ **October 1, 2013:** You must submit claims with ICD-10 codes only for services provided on or after this date.

AAHIVM credentials provide effective tool for combating Medicare billing scams

# FIGHTING FRAUD

## THE U.S. GOVERNMENT IS STRENGTHENING ITS CRACKDOWN ON PRACTITIONERS

who scam federal health care programs, with new muscle provided by the 2010 health care reform law and a determination to shut down fraudulent or erroneous federal health program claims that exceeded \$24 billion in 2009.

A number of these cases involve providers with questionable or no legitimate credentials who submit falsified claims for treating HIV patients, according to Michael B. Wohlfeiler, MD, JD, AAHIVS, who often testifies as an expert witness for the U.S. Department of Justice in HIV-related Medicare fraud cases in south Florida.

An HIV Specialist™, Dr. Wohlfeiler is medical director for special immunology services at Mercy Hospital in Miami Beach, FL. That program, with more than 2,500 HIV patients, provides Ryan White, Medicaid-waiver and other services to patients with HIV.

“As part of the preparation for an upcoming trial, I was asked by the U.S. Attorney how to determine whether a physician is an expert in the care and treatment of persons infected with HIV,” Dr Wohlfeiler said. “I immediately discussed the Academy’s HIV Specialist™ credentialing program.”

This latest request is not unusual, according to Dr. Wohlfeiler, whose medical career has largely been devoted to treating HIV patients. Judges, he said, often ask how to determine if a physician is qualified to treat HIV patients, and sometimes defense attorneys will challenge Dr. Wohlfeiler’s own credentials as he testifies against their clients.

“All of this illustrates the need for broad acceptance and recognition of AAHIVM’s HIV Specialist™ certification by governments and other authorities,” he said. “Because anybody can hold themselves out as being an HIV expert and treater. And it happens.”

### Feds Fight Back

While the government’s crackdown recently has grown in intensity, anti-fraud cases have been brought for the past

several years and, according to Daniel R. Levinson, inspector general at the U.S. Department of Health and Human Services (HHS), often target acts committed by criminals who masquerade as Medicare providers and suppliers but do not provide legitimate services or products.

Testifying before the House Energy & Commerce Health Subcommittee September 22, Levinson said the new Affordable Care Act (ACA) requires HHS to establish procedures for screening providers and suppliers participating in Medicare, Medicaid, and the Children’s Health Insurance Program.

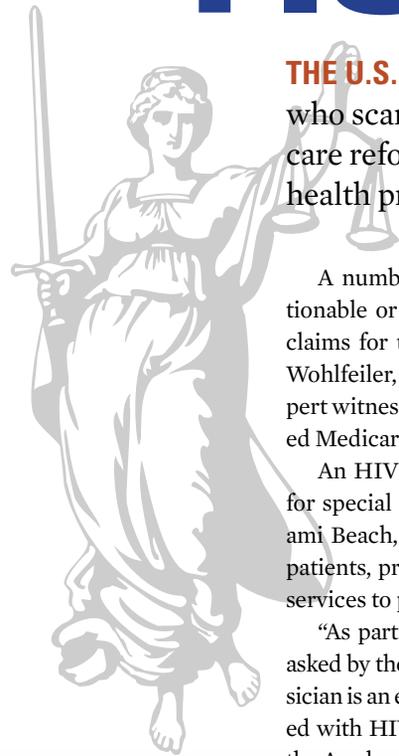
“At a minimum, providers and suppliers will be subject to licensure checks,” he explained, in addition to other screening measures based on risk, including fingerprinting, criminal background checks, multi-state database inquiries, and random or unannounced site visits.

That, of course, is just part of the current anti-fraud initiative, which also includes stiffer penalties for violators and the use of a new Data Team to support the work of an anti-fraud task force. The Data Team uses high tech tools and criminal intelligence to identify locations where billing for certain services is more than 10 times the national average. Currently, Medicare Fraud Strike Forces have been established in seven fraud hot spots – Miami, Los Angeles, Detroit, Houston, Brooklyn, Tampa, and Baton Rouge.

### Phony Billing, No Care

The HIV-related cases in which Dr. Wohlfeiler has testified have mostly involved criminal charges brought by the feds against clinics and physicians for allegedly defrauding Medicare by billing for HIV therapies that were medically unjustifiable and fraudulent.

BY BOB GATTY



DLEWIS33 / ISTOCK



The alleged fraud mostly revolved around parenteral therapies such as Procrit, Neupogen, IVIG, WinRho, Fuzeon and others, with evidence showing that patients often were paid to sign papers stating they received treatments when they had not. Lab samples were tampered with to obtain results that would justify the treatments, he said, and fake pharmacy invoices were created.

Often, Dr. Wohlfeiler said, defendants billed Medicare for infusion therapies that should not have been prescribed, that were excessive in number, amounts and frequency, and “patients never seemed to get better.” Some of the drugs, he said, were rare and expensive medications that were contraindicated for immune-suppressed patients.

In one case, Dr. Wohlfeiler said claims for more than 220 visits for one patient who supposedly received infusion were filed with Medicare. This patient was paid between \$100 to \$200 each time he signed into the clinic.

“They came to sign in and get their money,” he explained, “not to get treatment. There was absolutely no attention paid to their underlying HIV. So if these patients were not in HIV care elsewhere, they were in danger of dying. And a lot of these patients did have legitimate HIV doctors who had no idea they were going to these clinics.”

The scams, Dr. Wohlfeiler said, often are perpetrated by individuals with questionable licenses and no expertise in HIV care. In one case, the provider was a retired gynecologist; in another, a retired surgeon. “They don’t have any background in HIV at all and are not legitimate HIV treaters. But these scams generate large amounts of money, with one operation alone estimated at bringing in \$120 million,” he recalled.

“So far, all the trials I’ve participated in have resulted in convictions of all defendants on all counts and some of the sentences have been stiff, with one physician sentenced to 30 years in prison,” he said.

While the feds are getting tougher at rooting out these scams, having a nationally recognized way to determine the

qualifications of HIV treaters is critical to the success of many of these cases, Dr. Wohlfeiler stressed.

That, of course, is where the AAHIVM credentialing program comes in, and, in fact, was a major reason why the Academy was launched a decade ago.

As the established professional standard of HIV care and treatment, AAHIVM’s HIV Specialist™ and HIV Expert certifications are the first and only credentials offered to physicians (MDs and DOs), nurse practitioners, and physician assistants specializing in expert level HIV care.

Providers may achieve the HIV Specialist™ (AAHIVS) or HIV Expert (AAHIVE) designation after meeting strict eligibility requirements, and successfully completing a rigorous, psychometrically sound, knowledge-based exam on HIV-specialized medical care.

Peter M. Fox, director of credentialing at AAHIVM, stated that the field of HIV care has a number of unique challenges. These, he said, include “the fact that it spans many of the traditional medical specialties such as infectious disease, internal medicine and family practice.”

Moreover, he pointed out that the HIV care workforce is shrinking, and “is burdened with a well-known reimbursement inequity problem, being a highly time consumptive, procedure barren area of practice.”

The Academy’s certification program is intended to help address these challenges in a variety of ways, Fox said, as well as providing a reliable mechanism for patients to identify quality care.

For more detailed information, please visit [www.aahivm.org](http://www.aahivm.org) or contact [credentialing@aaahivm.org](mailto:credentialing@aaahivm.org), or 202-659-0699, ext. 13.



Michael B. Wohlfeiler, MD, JD, AAHIVS



HIV



# THE HIV CARE TEAM

BY BOB GATTY

**MEN AND WOMEN WITH HIV IN AMERICA** are generally living longer and better, thanks largely to advances in drug therapy. However, complimenting these medical advances is a shift in the overall treatment paradigm. Very often, effective HIV care tends to focus on the disease *and* other factors of daily life that can affect the patient's outcome.

Many experts recognize that simply providing medical treatment of HIV is limited. Many other factors, like mental health and nutrition, directly influence adherence to prescribed drugs, and thus can dictate the success or failure of treatment.

In an effort to support patients' various needs, many clinics now offer a one-stop shop approach to care, providing patients with as many services as possible to minimize stress, increase convenience and maximize adherence. In these settings, staff is available to help with support services such as transportation, housing, mental health counseling and addiction.

For some in the Ryan White community, this coordinated model of care is known as a medical home. Born out of the growing need to synchronize medical and social services for HIV patients, the Ryan White medical home concept offers patients a variety of services in one institution.

For the medical providers, this model provides an opportunity to coordinate patients' care with mental health professionals, case managers, nutritionists and others.

"We feel the multi-disciplinary approach is the most effective model for patients with any chronic illness," said Michael Virata, MD, FACP, AAHIVS, an infectious disease physician at the Haelen Center at the Hospital of Saint Raphael in New Haven, CT.

Located in the Family Health Center at the hospital, the Haelen Center provides social services, education, pastoral care, counseling and testing for patients with HIV.

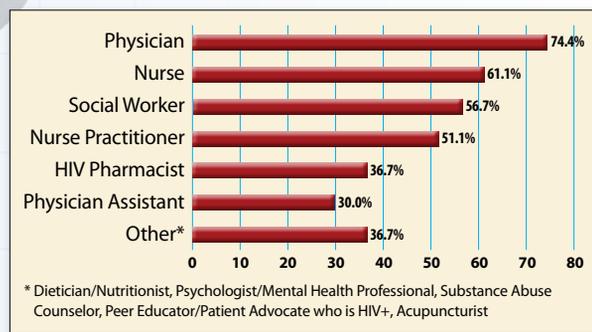
"The patient really appreciates the fact that we try to get as much as possible accomplished," stated Dr. Virata. "It's the one-stop shopping idea, and it is specific to our patient population here."

Clinics following this same approach offer a variety of services, either through in-house staff or contract professionals. Those services also can include pharmacists, dieticians, nutritionists, massage therapists, and acupuncturists.

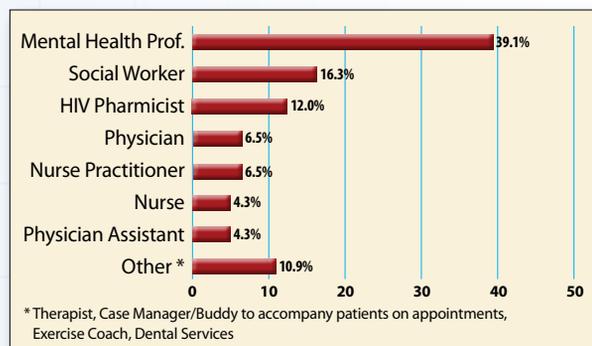
## Widespread Adaptation

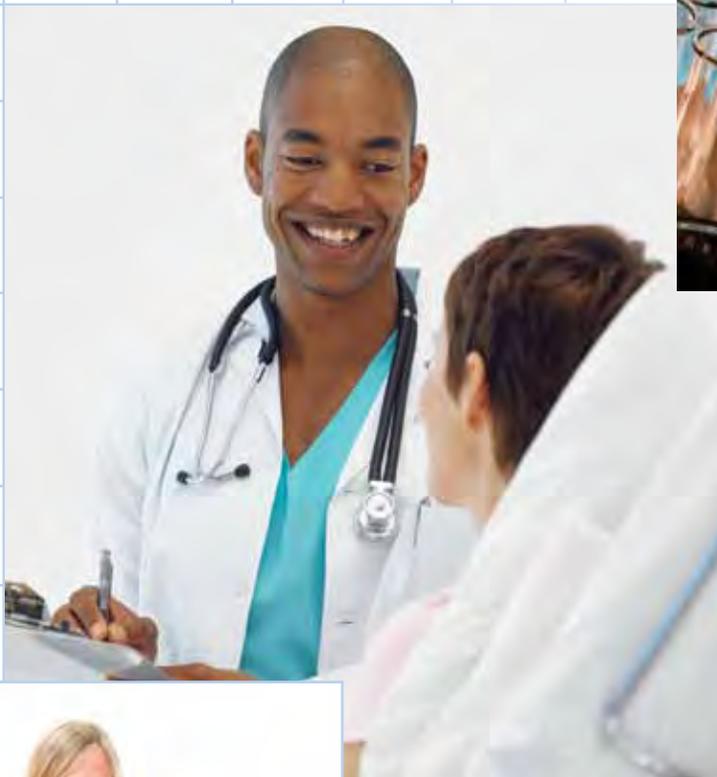
Earlier this year, AAHIVM surveyed members to assess the extent to which the team approach to HIV care is being implemented across the nation. The results indicated widespread adaptation, and in cases where this is not the case, more than 84 percent of respondents said it would be beneficial if a more comprehensive team could be established.

Asked what other HIV practitioners work in their practice, members responded as follows:



When asked what additional team member they would like to see added to best serve the team and patients, the response was as follows:





problems, we reach out to the clinic staff to help set up a plan according to their needs. We do this every month to fill in the gap between clinic visits.”

“We also deal with social issues that might be a barrier to adherence,” Hunt explained.

“If clinics don’t have social workers or specialty care managers, we have case management staff here to help work on these issues. It is all part of our mission.” CCN even arranges for transportation for patients who have no other means to get to their appointments.

Pharmacy Director, Jeff Meis pointed out that in addition to filling HIV/AIDS prescriptions, CCN also fills other prescribed drugs for its contracted clinics. “We like to get the entire drug profile so we can check for all potential drug interactions,” he explained. “Also, when we contract with a clinic, we have pharmacists they can call any time, 24/7, to get a quick answer.”

CCN’s follow-up calls to patients every 25 days (at a minimum) allow them to set up delivery and obtain up-to-date, ongoing information about the patient’s adherence. “In those phone conversations, we can talk about whatever the patient wants to discuss and can learn if the patient needs help in any other way. We then pass that information on to the clinic. So we end up being an extension of their team,” Meis said.



Largely, the lack of resources is the major reason why more facilities have not been able to build a more comprehensive HIV team. More than 88 percent of respondents said a shortage of funding was the primary barrier.

### Key Resources

Circumventing the funding barrier can be cumbersome. However, there are unique approaches to building a more robust team environment. For instance, working with a contracted 340B pharmacy such as the

Pittsburgh, PA-based Coordinated Care Network (CCN) is an efficient way to incorporate more members onto an HIV care team. This type of partnership gives providers the opportunity to work with pharmacists and specialty care representatives best suited to meet the needs of their HIV patients.

“The process starts when the clinic sends us a prescription and patient demographics. One of our pharmacists checks for drug interactions and duplicate therapies and processes the prescription. Then, we assign a dedicated specialty care representative to work one-on-one with the patient. The specialty care representative contacts the patient to review shipping needs, both to protect confidentiality and to make sure the medications arrive when they are needed,” explained Lori Hunt, RN, CCN’s clinical director.

“About five-to-seven days before refills are due, we call every patient to verify their profile. We talk to them about their meds and any barriers to adherence,” she said. “If we hear of

### Putting 340B Funds to Work

In addition to providing the patient with optimal care and continued follow-up, the CCN model can also generate revenue for the clinic, allowing the opportunity to expand the internal HIV care team.

The Ryan White Clinic at the Family Medical Center in the Conemaugh Health System, Johnstown, PA, this year launched its 340B program and, according to Janet Sawyer, CRNP, AAHIVS, has already earned enough profit to hire a part-time social worker. Although it took two years to get the program approved and underway, it has already paid off by allowing the clinic to strengthen its HIV care team.

The Family Medical Center is a family practice that serves all patients. But the Ryan White Clinic there has this mission: “Committed to providing the highest quality health care to the rural HIV population using a team approach of health care professionals along with patient input devoted to increase the wellness, dignity and health care of our patients.”

There, the team, coordinated by Sawyer, includes physicians, an HIV pharmacist, dietician, nurse practitioner, and medical case managers. “All of the aspects of the patient are looked at,” Sawyer said.

To illustrate the program’s success, Sawyer pointed to a patient who has been HIV+ for the past 15 years.

“He came to us from another practice five years ago,” Sawyer said. “He had neuropathy, some apparent mental deficits, and his viral load was not under control. Our infec-

tious disease physician worked with him. Our pharmacist analyzed his meds and came up with another regimen. Our dietician looked at his diet—he has diabetes—and made some suggestions. Wenche Bonini, one of our medical case managers, and I visited him and set up pillboxes and transportation. Now, his viral load is undetectable. He is eating better, and cognitively, we have seen another side of this man. He reads novels. He is doing well.”

### Treating the Whole

All across the country, this new style of treating the whole patient versus just the disease is showing great strides. For instance, many clinics now include nutritionists or dieticians as part of their team to help patients improve their overall health and deal with other health issues.

“Nutrition goes along with a healthy life style, so it is great for patients to be able to talk with a nutritionist directly for any help,” Dr. Virata agreed.

The Haelen Center clinic even includes a smoking cessation counselor “because we realize how significant smoking relates to co-morbid conditions, especially with advancing age, like hypertension, coronary artery disease, and malignancies. Smoking cessation has a significant impact on the overall health of the patient.”

At Pride Medical Inc. in Atlanta, a team that includes physicians, a psychotherapist, nurse practitioners, nurses, and a massage therapist, offers successful patient care, stressed Juli Eschenbach, PharmD, AAHIVE.

“I can very easily say to a patient, ‘let’s make an appointment with our psychotherapist.’ I have the ability to refer to someone I know and trust. I feel like I’m making the utmost contribution because I have all of those pieces that I can tap into,” she said.

In Boston, an HIV team at Boston Health Care for the Homeless provides comprehensive primary care to more than 300 patients and offers case management and client advocacy services to dozens more. There, the team is comprised of physicians, a physician assistant, a nurse practitioner, nurses, behavioral health professionals, dentists and case managers. They provide a model of care that integrates primary care, behavioral health, oral health, case management and HIV services.

“All of us feel we couldn’t do the work we do with this patient population without this comprehensive team,” said Carol Hohl, PA-C, MHS, AAHIVS. “Our patients have so many needs separate from their medical needs, and addressing them is the key to succeeding in their care. Here, there is always somebody available to see them.”

At Boston Health Care for the Homeless, nurses and case managers meet weekly with patients regarding such concerns as housing and substance abuse, Hohl said. “It keeps them really connected to the patients.”

Now, the program is hoping to add a pharmacist to its team to help with adherence and other needs regarding medications. Over 60 percent of patients there use illegal

drugs, “so we really need specialized support and care to keep them adherent,” Hohl explained. “We’ve been able to put this team together and see it grow and our patients flourish. That is very rewarding.”

### Benefits of On-Site

Many clinics rely on larger health care facilities to provide extensive support to their program, even if these outside professionals do not work exclusively with HIV patients.

For instance, the Haelen Center relies on hospital mental health professionals. “If we had a psychologist or therapist at the clinic to do initial psych evaluations, it would be much more beneficial for overall patient care,” said Dr. Virata. “Yes, we can refer to the hospital mental health department, but it is a little bit more difficult.”

He said his facility is hoping to have funding soon for both mental health and substance abuse counseling services.

Cameron Wolfe, MD, works at two clinics affiliated with Duke University—one a large facility in Charlotte, NC, where a broad, comprehensive team is available, and the other in Fayetteville, NC, where physicians from the Duke facility are sent to supplement local staff.

“The ability to offer perfect care to patients is limited by your ability to control all of the services needed to address their many and complex needs,” he said. “I would hate to give the impression that it is necessary for smaller services to have all of these people, but it certainly is an advantage. We do not have the same luxury in Fayetteville.”

Especially helpful at the Charlotte facility, he said, is the on-site addiction specialist who counsels patients with drug and alcohol problems, including depression and dependency, and who helps to triage patients into psychiatric care, when needed.

“I would love to have that service in Fayetteville, too,” Dr. Wolfe said. “That clinic (which serves a large population of low income patients) would be well suited to have that expertise. As it is, counseling there is more limited and it’s harder to get people linked into services.”

The team approach—the ability to focus comprehensively on all of the factors that affect HIV patients—is a huge advantage in achieving success, Dr. Wolfe said.

“Many people, by the time they reach our clinics, have many more issues going on besides their HIV that need to be addressed,” he said. “Does it help to improve adherence? Absolutely. Does it help to get patients back on the road to success? Absolutely. Some people have so many issues that we can have a far better outcome if we can identify, and confront each of their issues with a multi-disciplinary team. You achieve much better outcomes if you can address all of these issues facing your patients. It makes an enormous difference.” **HIV**



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# The **HIV** Dream Team

BY BOB GATTY

*What would an “all star” team of providers look like?*

**COMPREHENSIVE CARE CLINICS ARE CONFIGURED IN MANY WAYS**, with the specialties included often depending upon the setting and available funding. Preparing for this issue, *HIV Specialist* interviewed providers across the country who currently work in team settings and who contribute to the care and wellbeing of HIV patients.

The men and women listed below represent a vast array of collective expertise. These dedicated professionals would be welcomed additions to any team anywhere.

So, meet the members of the *HIV Specialist* “Dream Team:”



“As a physician on the team, you are expected to lead and guide the patient through the process and refer as needed, I encourage my patients to tell me what they need.”

– Dr. Michael Virata



Dr. Lara Strick

## Physician

Michael Virata, MD, FACP, AAHIVS, and Lara Strick, MD, MSc, treat patients in vastly different facilities and settings. Dr. Virata works at the Haelen Center HIV/AIDS clinic at the Hospital of Saint Raphael, New Haven, CT, while Dr. Strick is a traveling physician, covering all of the prisons in Washington State and also working at a Ryan White clinic in Seattle.

“As a physician on the team, you are expected to lead and guide the patient through the process and refer as needed,” Dr. Virata said. “I encourage my patients to tell me what they need.”

Dr. Virata acknowledged that many patients have primary care issues that need to be addressed, and so he looks for help from a general internist who works with the clinic part time, or consults with other colleagues at the hospital.

While the hospital provides a good deal of support, including mental health assistance and pharmacy support, the clinic includes full time and part time physicians, a physician assistant, nurse practitioner, nurse, social worker, nutritionist, and a smoking cessation counselor.

For Dr. Strick, 80 percent of her time is spent taking care of prisoners and training other physicians who treat them. She regularly visits nine of the prisons scattered throughout the state and estimates that she sees about 140 individual inmates each year.

The challenges are many, including a higher than normal rate of co-morbidities, including mental illness, hepatitis, drug addiction, and psycho-social issues. “There are a lot of unique issues regarding stigma and confidentiality in prisons that relate to treatment and success,” she said. “But if you have a good relationship with patients, you can have success. Greater than 90 percent of our patients’ [viral] loads are currently undetectable.”

Important components of her prison system team are the release planner and prevention counselor who sees inmates about six months prior to their release, with the goal of linkage to care and reducing the risk of them spreading the disease when they are re-integrated into their community. Unfortunately, she said, many eventually return to the prison and back to her care.

"I am a breast cancer survivor. I worked for 13 years not knowing why I was driven to care for HIV patients. But when I got cancer, I learned how to survive. Then I realized what drew me to my patients—they are survivors."

— Dr. Sherry Meltz

### Psychotherapist

Sherry Meltz, PsyD, a psychologist at Pride Medical Inc., Atlanta, has been working with HIV/AIDS patients for 23 years, bringing a personal connection and affinity to her work in treating this "community of heroes."

"I am a breast cancer survivor," she explained. "I worked for 13 years not knowing why I was driven to care for HIV patients. But when I got cancer, I learned how to survive. Then I realized what drew me to my patients—they are survivors."

Dr. Meltz' best friend and business partner died of AIDS, she said, providing further motivation for her work.

"Managing chronic illness and depression and working in the community, I have learned more than what I have taught," she said.

Dr. Meltz was recently appointed president-elect of the Board of Directors for the 2012 Southeast Regional Gay Men's Health Summit, and has been a board member for nearly three years.

"My doctorate is in psychology," she said, "but I treat a lot of addiction, as well as depression, anxiety, and panic disorders. All of my clients are gay men." Her caseload at Pride Medical is about 55 patients.

Dr. Meltz said she started Heartsong Southeast, a retreat that each May brings positive men and women from five southeastern states together with HIV providers and others who work with the pandemic we know as HIV disease.

Her philosophy "has always been that mind, body and the spirit must coalesce for healing, and that any one part missing will not promote total wellness," she said. "Pride Medical treats patients and clients with that mission, and it is a great one."

### Addiction & Mental Health Therapist

Keith McAdam once was homeless and on drugs. And then, he said, "One day I hit 30 years old and realized I was still alive—despite what I was doing to my body. So I decided I needed to do something about it."

He did.

Today, McAdam, LCSW, LCAS, is a clinical instructor and behavioral health provider—an addictions and mental health counselor—at the HIV clinic in the Duke University Health System in Durham, NC, where he uses his own life



experience to assist addicts afflicted with HIV.

"I've been involved with HIV work since my early 20s," he said, "because I started losing friends to HIV in the late '80s. I have had my own hurdles to overcome, which is what got me into addiction in the first place. But I can put this to use by connecting with, and helping, addicts."

It's much easier, explained McAdam, now 43, for addicts to accept treatment from another addict. There is an understanding, a connection, that can only come from experience.

"I've been battling dependency since I was a kid," McAdam said. "I can say, 'Yes, I've been there.' I don't have personal experience with HIV, but it's been part of my life. I've made a lot of major behavioral changes over time, and I don't use substances any more. I want to help others do the same."

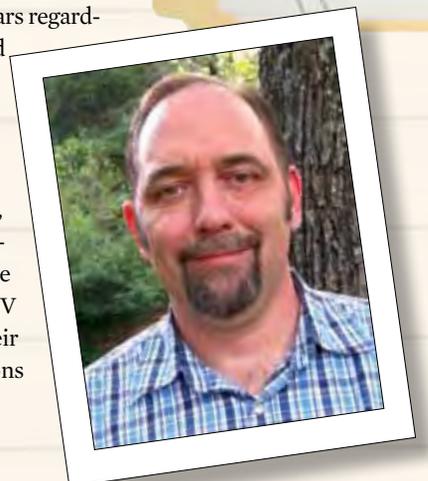
McAdam said the clinic at Duke uses a "harm reduction-based" program, not a "12-step" program because many of the patients there simply can't deal with an "all or nothing" approach. "They just can't stop using and stay on the program." So the approach is to reduce their dependency over time.

Now, McAdam says much of his work is focused on helping patients manage the chronic pain that is common among HIV patients—and difficult to treat because they are addicts.

"In a way, they get a raw deal," he said. "Crack cocaine addicts will sell their prescription narcotics to feed their habit, so a lot of times clinics won't take these patients. But we have contracts with them, and that means they have to participate in a recovery program. They will see me so we can communicate face-to-face, and I can keep the doctors current on what patients are doing day-to-day."

McAdam is co-author of a soon to be published paper, "A Cross-site, Comparative Effectiveness Study of an Integrated HIV and Substance Use Treatment Program." The paper reports on data over the past five years regarding the effectiveness of an integrated team approach to treating HIV patients who are also addicts.

"The more integrated the system is, the better the outcomes are, including substance abuse, health, and mental health," McAdam said. "Patients do better if we can fully integrate care so that HIV doctors can be informed about their patients and make better decisions regarding their care."



"I've been involved with HIV work since my early 20s, because I started losing friends to HIV in the late '80s. I have had my own hurdles to overcome, which is what got me into addiction in the first place. But I can put this to use by connecting with, and helping, addicts."

— Keith McAdam

"At our practice, the pharmacist can see anybody. We know our patients and will do everything possible to provide whatever help they need. I really love what I do, and I like to think my patients love me back for it. I do what I can do."

– Juli Eschenbach



### Pharmacist

It is a major advantage for clinics to have their own pharmacist to help patients with every aspect of their drug regimen and to avoid interactions with other prescription medications.

Juli Eschenbach, PharmD, AAHIVE, is a staff pharmacist for Pride Medical Inc. in Atlanta, which operates an independent pharmacy while providing pharmaceutical services to patients.

"We make sure our patients are compliant," she said, explaining that there are monthly calls to patients to determine if there are any problems that need to be resolved or if the patient needs to see a doctor for any reason.

They also help patients find the money to pay for their medications. "We are very aggressive with co-pay cards" to help patients afford their meds, working with the pharmaceutical companies to obtain assistance, Eschenbach explained.

The Pride Medical pharmacy provides free delivery to patients, with drugs arriving in plain boxes to avoid any concerns about privacy. "We use a delivery service in the metro area but we also deliver in surrounding states," she added.

"At our practice, the pharmacist can see anybody. We know our patients and will do everything possible to provide whatever help they need," said Eschenbach. "I really love what I do, and I like to think my patients love me back for it. I do what I can do."

For some clinics, the best approach is to take advantage of a contracted 340B pharmacy service. Jeff Meis, pharmacy director at the Coordinated Care Network, based in Pittsburgh, PA, says CCN works with its clients to help them seamlessly serve their patients—almost as if they had a pharmacist on staff. Pharmacists regularly consult with patients and clinic staff, and routinely arrange specialized services to meet patients' needs.

He points out that CCN's central pharmacy and mail order facility provides 340B Covered Entities, including Ryan White Part C & B clinics, Federally Qualified Health Care Centers, and Disproportionate Share Hospitals, with specialized services tailored to their individual clinical needs.

### Physician Assistant

Carole Hohl, PA-C, MHS, AAHIVS, has worked in HIV care since 1990 and at the Boston Health Care for the Homeless Program (BHCHP) since 1997.

"It is very rewarding to be able to see changes that have taken place," she said, "to see people able to live and function well today despite their disease."

A primary care clinician, Hohl cares for about 60 HIV patients as well as many non-HIV infected patients. "I manage the team, supervise the staff,

manage our federal and state grants, while serving as a staff advisor to the Consumer Advisory Board, a group of patients that gives advice and feedback to the program.

"We've been able to put this team together and see it grow and see patients flourish," Hohl said. "It is very rewarding."

While the team at her facility is substantial, the clinic is working to find the resources to add a Spanish speaking mental health provider who can work with the 25 percent of patients there who speak Spanish, many of whom speak *only* Spanish.

"We at BHCHP also have a 340B Pharmacy, and we hope to incorporate one of the pharmacists into the team in the near future," she said.

"We have a medical respite facility in the same building as the clinic, so people who are too sick for the street can go there," she added. "It's part of our team approach." There is a mental health intervention program, as well.

Major sources of funding for Boston Health Care for the Homeless include Medicaid, the Ryan White program, and money from the state of Massachusetts. She is concerned about possible cuts in funding from both Medicaid and the state, given the current economic environment.

"Although my clinical work gives me great satisfaction and I adore my patients, I am really most proud to have been able to develop this team over the years," she said. "We have top notch nurses and case managers who work long hard hours keeping patients in care. Our medical and mental health providers are excellent. Working with a population where over 80 percent have either a mental health or substance abuse diagnosis is extremely challenging, but each member of the team is ready to do what it takes to care for the patient and support their co-workers."

### Nurse Practitioner

Janet Sawyer, CRNP, AAHIVS, is a key member of the team at the Ryan White Clinic at the Family Medical Center in Johnstown, PA, where she has been working ever since the Center received its Ryan White grant eight years ago.

She is a strong advocate of the team approach to care, and stresses the important contributions made by the entire unit, for which she functions as coordinator.

Sawyer likes to emphasize the work of her teammates—the dietician, the



"I'm known as 'Miss HIV.' I'm the person the patients know as the one constant at the clinic—the person they can come to whenever they need help."

– Janet Sawyer

pharmacist, physicians, psychologist, case managers. But clearly, Sawyer is the glue that keeps the team functioning smoothly and effectively—just like many of her nurse practitioner colleagues who care for HIV patients across the nation, 24-7.

“I’m known as ‘Miss HIV,’” she said. “I’m the person the patients know as the one constant at the clinic—the person they can come to whenever they need help.”

Because the Family Medical Center serves many patients, not just those with HIV, patients come for help with a wide variety of illnesses and concerns. Among those are patients with HIV, who often are there for treatment of other conditions.

“While they are here, I check with them to see if there is anything we need to do for them as far as their HIV is concerned,” Sawyer explained. “I check to see who is deficient in their appointments and who needs a little boost in getting in here for that.”

This week, a patient lost his health insurance. “We have to get him through that crisis,” she said, running through some of the options they need to consider and steps they need to take. “A lot of what I do is driven by patients and their problems.”

Every day is full. Her job includes: new patient intake, including physical status and health history assessment, and a needs assessment; educating patients, especially those with a new diagnosis; referring patients for supportive services; reviewing labs and following up with physicians regarding plan of care; assessing medication adherence and interventions, and referral to pharmacist as needed.

And that’s just half of her list of responsibilities that also includes presenting at support groups, monitoring the 340B drug program, refilling prescriptions and reviewing charts to ensure overall care guidelines are being met.

“Patients have my direct line,” she said. “If they are having a problem or need to contact their physician, they call.”

### Medical Case Manager

Wenche Bonini also works at the Family Medical Center in Johnstown, PA, providing supportive services for HIV patients, work that is critical to successful outcomes.

Bonini said her job is to “break down barriers” for patients—to help find housing, arrange transportation, or provide emergency assistance when it is needed.

“We try to stabilize their lives,” Bonini said. “If their lives are not stable, it’s hard to keep



“We try to stabilize their lives. If their lives are not stable, it’s hard to keep them in medical care.”

– Wenche Bonini

them in medical care.”

They help with patients’ health insurance, resolving issues and “jumping through hoops” so patients don’t have to.

Home visits are common, especially for patients who are home-bound. Outreach, education, adherence counseling—all become part of their job.

Bonini convinced local schools to allow her to provide HIV 101 programs, either in classroom settings or even larger assemblies. “Many students here have been in denial about HIV,” said Sawyer, “but she has been able to get into the schools.”

Now, teachers call and ask her to come in for a talk, so she does—often bringing a patient with her to provide a personal perspective.

### Specialty Care Representative

Frank Butala, specialty care representative at Coordinated Care Network, has similar responsibilities, all geared towards helping the patients served by the clinics that contract with CCN for its 340B Specialty Pharmacy Services.

“The key,” he said, “is to identify the barriers that exist—and to find a solution. We do whatever is necessary in working with the clinic and the patient to come up with a plan. We view ourselves as an extension of and an agent for the clinic.”

“An important part of my role is the one-on-one relationship that I develop with clients and patients,” he said.

“At the beginning of the day, I have a computer generated list of patients to call—those who are due to have refills within the next five to seven days,” he explained. “Every patient is absolutely different from the next. When we speak with patients, we get updated information on insurance and any changes in demographic information. We pass that along to the clinics so they know exactly how to contact the patient. It makes their job easier.”

Butala says he and other specialty care reps at CCN seek to resolve any issues the patient might have. Even problems like getting medication to patients who are traveling and are without their meds fall to Butala



“The key is to identify the barriers that exist—and to find a solution. We do whatever is necessary in working with the clinic and the patient to come up with a plan. We view ourselves as an extension of and an agent for the clinic.”

– Frank Butala

"I talk to patients about nutritional issues that they might have, from accessing food, such as finding a food bank, to applying for food stamps, or talking with new diabetes patients about insulin and their diets."

— Ben Atkinson



Leah Baxter

and his colleagues. "I can get the meds to them the same or next day," he said. "That's a good thing."

When Butala learns that a patient has lost insurance, he lets the clinic know and offers assistance in finding alternative coverage. "It helps us and the clinic and the patients," he explained. "The whole program is focused solely on the patients. We give them every opportunity to succeed."

### Dietician

Another key member of the HIV team is the dietician, the expert who helps patients with complicating factors such as diabetes manage their diets, or gain access to food, or even obtain help with meal preparation concerns.

For example, Leah Baxter, the dietician at Family Medical Center, helps patients with swallowing difficulties select and prepare foods that are more easily consumed.

"I'm available here to provide nutritional services to every patient who needs it," she said. "I see patients when they have problems, and by working with other team members, like the pharmacist, we find solutions."

Ben Atkinson, MS, RD, CD, is the dietician at the Madison Clinic in the Harborview Medical Center in Seattle, a primary care clinic for HIV patients.

"I talk to patients about nutritional issues that they might have, from accessing food, such as finding a food bank, to applying for food stamps, or talking with new diabetes patients about insulin and their diets," he explained.

Atkinson pointed out that some HIV medications have nutritional implications; so he meets with the clinic's health educator, case manager, physician and pharmacist to help find solutions.

"This morning, two new patients were here to see the doctor, and he knew they had nutritional

issues. So the doctor said, 'Let's go see Ben and discuss this,' and we got it done. We're all here to refer to each other daily—to help patients get the care they need."

### Massage Therapist

James Dustin, the massage therapist at Pride Medical Inc., provides an essential service to HIV/AIDS patients who suffer from stress about their overall health status as well as from pain resulting from their disease or their medications.

"I do a lot of clinical work—people with specific conditions—in addition to relaxation therapy," he said. "You have to have a patient be relaxed to provide effective treatment. So I encourage relaxation therapy."

Dustin pointed out that many HIV patients suffer from myalgia, aches and pains over the entire body. Often, there is nerve damage that either results from the disease or, perhaps, as a side effect of some medications.

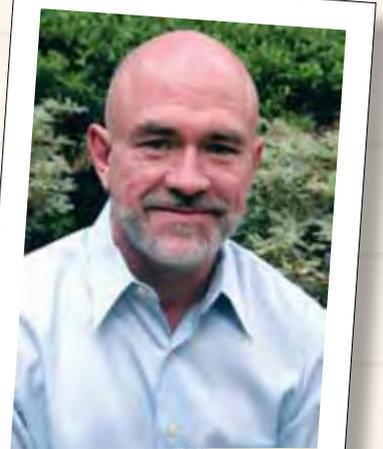
"Massage can't cure that, but it is effective for pain management and helping you feel better," Dustin said. "HIV survivors have a higher rate of spinal disc issues, and so I see a lot of patients with these problems."

He points to studies that indicate that regular massage, 45 minutes twice a week, increases CD4 and CD8 cells and reduces neuropenefrin output, which controls mood. "Regular massage keeps more of that in your body," he said. "It's almost like a natural antidepressant."

Many HIV patients lack human contact, something that everyone needs, Dustin added. "I might be the only person who actually touches them," he said. "After a few visits, I can see the difference."

Dustin knows. He is HIV+. He understands stigma and what it can do. He's been doing this for nine years, now, working in an HIV practice.

"I find it very rewarding," he said. **HIV**



"I do a lot of clinical work—people with specific conditions—in addition to relaxation therapy," he said. "You have to have a patient be relaxed to provide effective treatment. So I encourage relaxation therapy."

— James Dustin



# Advances in HIV Prevention and Increased Use of ARVs in Prevention Research

**L**AST OCTOBER SAW the first encouraging report on the development of an effective HIV vaccine. Vaccination with ALVAC and AIDSVAX resulted in a 26.4 percent reduction in risk of HIV acquisition among 16,402 participants in Thailand.

However, this report was soon followed in December by a disappointing prevention study (MDP 301) that found no evidence that a topical microbicide (0.5% PRO 2000) reduced HIV acquisition. This study, which enrolled 9,385 women, failed to confirm a promising result from a smaller study, HPTN 035, which found a 31 percent reduction in HIV acquisition with the same microbicide. Due to the discouraging results of prior vaccine and microbicide trials, attention has shifted to antiretroviral drugs (ARVs) for prevention.

There are several ongoing trials using ARVs to prevent HIV infection, either topically or systemically.

The first to be concluded, CAPRISA 004, reported a 39 percent reduction in HIV acquisition with the use of topical 1% tenofovir gel dosed within 12 hours prior to sex and once after. CAPRISA 004 also observed a 51 percent reduction in Herpes Simplex Virus (HSV) acquisition.

At the 18<sup>th</sup> International AIDS Conference this year, the CDC reported on the safety of oral tenofovir in HIV-negative people. Expectations are high for the first large oral pre-exposure prophylaxis (PrEP) study of Truvada (iPrEx), which is completing study visits in late 2010.

A large ongoing PrEP trial evaluating tenofovir gel, oral tenofovir and tenofovir/emtricitabine is VOICE (MTN 003), conducted by the Microbicide Trials Network. VOICE is comparing oral tenofovir and Truvada, and 1% tenofovir vaginal gel dosed daily, with both oral and gel placebo arms (overall five study arms). This trial is about one-third enrolled, with a target of 4,200 and results expected in 2013.

Due to the positive results observed in the CAPRISA 004 study, UNAIDS issued a call for increased funding to support several new trials and address additional questions about the use of tenofovir gel. The objectives of future studies will be to repeat the CAPRISA results in a variety of settings including with younger women. They will also evaluate different dosing schedules including a single application of the gel before sex, or failing that, immediately after intercourse, compared to the original two dose regimen.

Based on studies that suggest universal HIV treatment could significantly reduce HIV transmission, there has also been interest in the impact of HIV treatment on transmission. In the Partners in Prevention HSV/HIV Transmission Study, almost no HIV transmission occurred in the partners of HIV-positive people on antiretroviral therapy.

Of 3,381 couples, 10 percent of people with HIV initiated ART during the study. Only one of 103 genetically-linked HIV-1 trans-

missions was from an infected participant on ART and they had only recently started therapy.

An ongoing, fully-accrued study being conducted by the HIV Prevention Trials Network (HPTN 052) randomized serodiscordant couples with high CD4+ cells to receive ART to determine the effect on HIV transmission.

A pilot study (HPTN 065- Test and Link to Care Plus) will evaluate the feasibility of interventions needed to support a larger trial to study whether universal ARV treatment can significantly reduce HIV transmission. This study is being conducted in the Bronx, NY and Washington, DC.

Because tenofovir is used in most first-line regimens, there are concerns about the broader use of ART for prevention due to the potential selection of drug-resistant HIV. Also, if ARVs are prescribed for all HIV-infected people, there are concerns about cost, monitoring, and toxicity. The future looks to be one with more wide-spread use of ART for HIV-infected people, as well as ARVs for HIV prevention.

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## Will the Future Paradigm for HIV Treatments Change?

**S**INCE THE PROTEASE INHIBITOR ERA began in 1996, standard first-line therapy for persons with HIV has included two nucleoside reverse transcriptase inhibitors (NRTI) plus a protease inhibitor (PI).

Subsequent clinical trial data led to the FDA approval of nevirapine (1996) and efavirenz (1998) and supported these agents as comparable to a PI/NRTI combination as first-line therapy. The addition of the integrase inhibitor raltegravir by the DHHS guidelines in December 2009 [1] and its inclusion by the IAS-USA guidelines this past July [2] was the first significant change in the standards for first-line HIV therapy in about 10 years.

At the recent 18<sup>th</sup> International AIDS Conference in Vienna, Austria (July 18-23, 2010), we saw some provocative and impressive data using new combinations of antiviral agents, as well as additional data on PI monotherapy. I will summarize a few of the key studies which may impact the way we treat our patients over next several years.

Three studies evaluated NRTI-sparing approaches to initial therapy in treatment naïve patients. All of these trials are relatively small in sample size, so they should be viewed as exploratory rather than definitive. However, they likely will set the stage for future first-line HIV therapies that will look very different than our current three-drug regimens.

In the PROGRESS trial (n=206), lopinavir/ritonavir was combined with either tenofovir/emtricitabine or raltegravir. The inclusion criteria were no prior antiretroviral therapy, an HIV-1 RNA level of > 1000 copies/mL, and any CD4+ count. The primary endpoint was plasma HIV-1 RNA < 40 copies/mL at week 48.

The study found that 84.8 percent of the lopinavir/ritonavir plus raltegravir patients compared to 83.2 percent receiving lopinavir/ritonavir plus TDF/FTC attained HIV-1 RNA levels of < 40 copies at 48 weeks by intent-to-treat analysis. This difference of only 1.6 percent met criteria for non-inferiority.

The proportion of patients with undetectable HIV-1 RNA at weeks 2, 4, 8, and 16 was significantly greater in raltegravir

arm, as seen with other studies using this integrase inhibitor. The mean CD4 count increase was 245 cells/mm<sup>3</sup> with tenofovir/emtricitabine vs 215 cells/mm<sup>3</sup> with raltegravir although this difference was not statistically significant. More patients in the tenofovir arm had renal dysfunction (3.8 percent vs 1 percent) but lipid abnormalities were more frequent with raltegravir. [3]

The SPARTAN trial (n=94) compared atazanavir plus raltegravir twice daily to atazanavir/ritonavir plus tenofovir/emtricitabine.

The 24-week results by ITT analysis showed 74.6 percent of the atazanavir plus raltegravir arm had viral loads of < 50 copies/ml compared to 63.3 percent in the atazanavir plus tenofovir/emtricitabine arm. Mean CD4+ count increases from

Red Ribbon on the Parliament Building in Vienna during the Conference



baseline were 166 cells/mm<sup>3</sup> vs 127 cells/mm<sup>3</sup> respectively.

Similar to the PROGRESS trial, the raltegravir-containing regimen had a faster HIV RNA decline. The proportion of patients prematurely discontinuing the study treatment was similar in the two arms (9.5 percent vs 10 percent). However, despite this encouraging virologic and immunologic data, the sponsors decided to stop this study due to higher rates of grade 4 hyperbilirubinemia (21 percent vs 0 percent). [4]

The last of the NRTI-sparing studies, A4001078, (n=121) compared the standard first line regimen of atazanavir/ritonavir plus tenofovir/emtricitabine to atazanavir/ritonavir plus maraviroc. The maraviroc was dosed at 150 mg once daily. Patients were required to have R5 virus at screening and to have a CD4+ count > 100 cells/mm<sup>3</sup>.

Among patients treated with atazanavir/ritonavir plus tenofovir/emtricitabine, 89 percent achieved HIV-1 RNA < 50 copies/mL at week 24 vs 80 percent in the maraviroc plus atazanavir/ritonavir arm. The CD4+ cell count responses were similar with a median increase of 195 cells/mm<sup>3</sup> in the maraviroc arm vs 173 cells/mm<sup>3</sup> in the comparator arm.

The incidence of grade 3/4 adverse events related to hyperbilirubinemia was higher in the maraviroc arm at 26 percent vs 13 percent with the NRTI regimen. However, no resistance occurred among five patients with treatment failure (HIV-1 RNA > 500 copies/mL), nor did tropism “shift” take place. More data from this trial will be forthcoming. It was also noted by the presenter that maraviroc plus atazanavir/ritonavir will be studied in another phase III clinical trial. [5]

Protease inhibitor monotherapy trials have been both presented at several conferences and published with many showing surprisingly good results. [6]

At the Vienna meeting, 96-week data from the MONET trial was presented. The 48-week MONET data was presented at the 2009 IAS meeting and published in *AIDS*. [7] This study randomized 256 patients who had HIV-1 RNA of < 50 copies/mL for at least six months and no prior use of darunavir (DRV) or history of virologic failure to receive darunavir 800mg/ritonavir 100mg alone or darunavir 800mg/100mg ritonavir plus 2 NRTIs.

At 48 weeks, monotherapy with darunavir/ritonavir was non-inferior to standard therapy with this boosted PI and 2 NRTIs. The 96-week data did not look quite as good, but still was encouraging, since 81 percent in the 3-drug arm had viral loads of < 50 copies/mL compared to 75 percent in the the darunavir monotherapy arm.

However, if re-suppression of virus with intensification was included as “success,” then darunavir monotherapy arm was non-inferior at week 96 (92.1 percent vs 90.7 percent). [8]

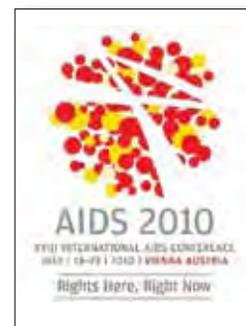
Although these studies did not provide outstanding out-

comes in all cases, I think they show that other safer, easier, and perhaps less costly therapeutic regimens can be used to treat HIV infection. I suspect in the next few years with the availability of newer combination therapies and additional data from the studies above, newer treatment paradigms including nucleoside-sparing will be adapted.

HIV

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# Together Everyone Achieves More in HIV Care

"IT HAS BEEN TOUGH since the fire," confided Veronica to social worker Jessica. "The smell of smoke in the apartment is awful; we lost our prescriptions; and then the telephone got cut off when we couldn't pay the bill. I feel so upset sometimes, I don't know how to go on."

When the care of families in crisis demands more than a simple prescription, can a multi-disciplinary team effort begin the process of healing?

It can, and it does.

"That feels much better now Berto," whispered little Cynthia, managing a smile between inhalations from the nebulizer. It was an unscheduled, but welcomed, visit for the preschooler, who had missed her prior appointment.



While I examined her and ordered medications to treat exacerbation of her reactive airways and lymphocytic interstitial pneumonitis, Berto, our nurse, translated details of history for Veronica, Cynthia's kinship foster mom, while administering the nebulizer. Meanwhile, Cynthia's nurse practitioner, Maggie, evaluated her chart, and while verifying medication refills with our pharmacist, Tony, discovered that antiretrovirals had not been refilled for the past two months.

While Jessica worked on emergency housing and telephone issues, Pete, our chaplain, provided pastoral support, and walked Veronica down to Steve, our staff psychologist for assistance with diagnosis and treatment of reactive depression.

Meanwhile, back in the treatment room, child life therapist

Jennifer provided playful diversion for Cynthia as Berto drew her blood. Later during play therapy, Molly, our nutritionist, uncovered the fact that there had not been much to eat at home since the fire. She got right to work, contacting the local church food pantry and arranging for a food stamp application.

Veronica reemerged with a smile from her meeting with Steve to receive discharge instructions from Berto and me, as Maggie rechecked Cynthia's breathing for a final time.

"The prescriptions should be ready now with Tony," I reminded Veronica as Cynthia and I shared a goodbye hug. "Now that the telephone will be on in emergency housing, please don't hesitate to call with questions or concerns."

As I turned and walked down the hall I thought to myself how very little I could do for Veronica and her family were it not for my sensational team.

Some children growing up with HIV infection in the United States have benefitted greatly from family-centered, child-friendly, multidisciplinary primary care with integrated HIV subspecialty services, offered by teams optimally consisting of pediatricians, pediatric nurse practitioners, nurses, pharmacists, social work case managers, child life therapists, psychologists, psychiatrists, nutritionists, chaplains, and other dedicated caregivers.

These team members have often developed long-standing and intimate bonds with patients and family members. The very strength of these bonds, forged by shared struggle against demons such as poverty and its associated calamities, social stigmatization, substance use, and all too often, the concurrent illness and death of multiple family members, has made it possible to begin to address the needs of such families in crisis.

In appreciation of the many issues bearing upon the lives of patients and families battling HIV, I would assert the importance of the family-centered, multidisciplinary care model for optimal HIV treatment throughout life. Indeed, together everyone achieves more!

HIV

• Patient and staff member names and identifying information have been altered to protect confidentiality.



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# KALETRA® lopinavir/ritonavir tablet, film coated

# KALETRA® lopinavir/ritonavir oral solution

## PROFESSIONAL BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

### INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The following points should be considered when initiating therapy with KALETRA:

- The use of other active agents with KALETRA is associated with a greater likelihood of treatment response.
- Genotypic or phenotypic testing and/or treatment history should guide the use of KALETRA. The number of baseline lopinavir resistance-associated substitutions affects the virologic response to KALETRA.
- Once daily administration of KALETRA is not recommended for any pediatric patients.

### CONTRAINDICATIONS

- KALETRA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) to any of its ingredients, including ritonavir.
- Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions.
- Co-administration of KALETRA is contraindicated with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance. These drugs are listed in Table 1.

**Table 1. Drugs That Are Contraindicated With KALETRA**

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA	Clinical comments
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents [see <i>Drug Interactions</i> ].
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
PDE5 enzyme inhibitor	Sildenafil <sup>a</sup> (Revatio <sup>®</sup> ) when used for the treatment of pulmonary arterial hypertension	A safe and effective dose has not been established when used with KALETRA. There is an increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope [see <i>Drug Interactions</i> ].
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam <sup>b</sup>	Prolonged or increased sedation or respiratory depression.

<sup>a</sup> see Drug Interactions for coadministration of sildenafil in patients with erectile dysfunction.

<sup>b</sup> see Drug Interactions, Table 7 for parenterally administered midazolam.

### WARNINGS AND PRECAUTIONS

**Drug Interactions - CYP3A Enzyme Inhibition** KALETRA is a CYP3A inhibitor. Initiating treatment with KALETRA in patients receiving medications metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already maintained on KALETRA may result in increased plasma concentrations of concomitant medications. Higher plasma concentrations of concomitant medications can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening or fatal events. The potential for drug-drug interactions must be considered prior to and during therapy with KALETRA. Review of other medications taken by patients and monitoring of patients for adverse effects is recommended during therapy with KALETRA.

See Tables 1 and 7 for listing of drugs that are contraindicated for use with KALETRA due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity [see *Contraindications and Drug Interactions*].

**Pancreatitis** Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations are a risk factor for development of pancreatitis [see *Warnings and Precautions*]. Patients with advanced HIV-1 disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

*Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.*

**Hepatotoxicity** Patients with underlying hepatitis B or C or marked elevations in transaminase prior to treatment may be at increased risk for developing or worsening of transaminase elevations or hepatic decompensation with use of KALETRA. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of KALETRA in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with KALETRA therapy has not been established. Appropriate laboratory testing should be conducted prior to initiating therapy with KALETRA and patients should be monitored closely during treatment. Increased AST/ALT monitoring should be considered in the patients with underlying chronic hepatitis or cirrhosis, especially during the first several months of KALETRA treatment [see *Use In Specific Populations*].

**Diabetes Mellitus/Hyperglycemia** New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

**PR Interval Prolongation** Lopinavir/ritonavir prolongs the PR interval in some patients. Cases of second or third degree atrioventricular block have been reported. KALETRA should be used with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of KALETRA with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of KALETRA with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended.

**QT Interval Prolongation** Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of KALETRA could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

**Immune Reconstitution Syndrome** Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis) which may necessitate further evaluation and treatment.

**Fat Redistribution** Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

**Lipid Elevations** Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides [see *Adverse Reactions*]. Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with KALETRA and HMG-CoA reductase inhibitors [see *Contraindications and Drug Interactions*].

**Patients with Hemophilia** Increased bleeding, including spontaneous skin hematomas and hemarthrosis have been reported in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

**Resistance/Cross-resistance** Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in KALETRA-treated patients, it is unknown what effect therapy with KALETRA will have on the activity of subsequently administered protease inhibitors.

### ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- PR Interval Prolongation, QT Interval Prolongation [see *Warnings and Precautions*]
- Drug Interactions [see *Warnings and Precautions*]
- Pancreatitis [see *Warnings and Precautions*]
- Hepatotoxicity [see *Warnings and Precautions*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adults - Clinical Trials Experience** The safety profile of KALETRA in adults is primarily based on 1964 HIV-1 infected patients in clinical trials.

The most common adverse reaction was diarrhea, which was generally of mild to moderate severity. In study 730, the incidence of diarrhea of any severity during 48 weeks of therapy was 60% in patients receiving KALETRA tablets once daily compared to 57% in patients receiving KALETRA tablets twice daily. More patients receiving KALETRA tablets once daily (14.4%) had ongoing diarrhea at the time of discontinuation as compared to patients receiving KALETRA tablets twice daily (6.18%). In study 730, discontinuations due to any adverse reaction were 4.8% in patients receiving KALETRA tablets once daily as compared to 3% in patients receiving KALETRA tablets twice daily. In study 802, the incidence of diarrhea of any severity during 48 weeks of therapy was 50% in patients receiving KALETRA tablets once daily compared to 39% in patients receiving KALETRA tablets twice daily. Moderate or severe drug-related diarrhea occurred in 14% of patients receiving KALETRA tablets once daily as compared to 11% in patients receiving KALETRA tablets twice daily. At the time of discontinuation, 19 (6.3%) patients receiving KALETRA tablets once daily had ongoing diarrhea, as compared to 11 (3.7%) patients receiving KALETRA tablets twice daily. Discontinuations due to any adverse reaction occurred in 4.3% of patients receiving KALETRA tablets once daily compared to 7.0% in patients receiving KALETRA tablets twice daily. In study 863, discontinuations of randomized therapy due to adverse reactions were 3.4% in KALETRA-treated and 3.7% in nelfinavir-treated patients.

Treatment-emergent clinical adverse reactions of moderate or severe intensity in ≥ 2% of patients treated with combination therapy for up to 48 weeks (Studies 863 and 730) and for up to 360 weeks (Study 720) are presented in Table 2 (treatment-naïve patients); and for up to 48 weeks (Studies 888 and 802), 84 weeks (Study 957) and 144 weeks (Study 765) in Table 3 (protease inhibitor-experienced patients).

**Table 2. Percentage of Adult Patients with Selected Treatment-Emergent<sup>a</sup> Adverse Reactions of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients**

	Study 863 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
	KALETRA 400/100 mg Twice Daily + d4T + 3TC (N = 326)	Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)	KALETRA Twice Daily <sup>b</sup> + d4T + 3TC (N = 100)	KALETRA 800/200 mg Once Daily + TDF +FTC (N=333)	KALETRA 400/100 mg Twice Daily + TDF +FTC (N=331)
<b>Endocrine Disorders</b>					
Hypogonadism	0%	0%	2%	0%	0%
<b>Gastrointestinal Disorders</b>					
Diarrhea	16%	17%	28%	17%	15%
Nausea	7%	5%	16%	7%	5%
Vomiting	2%	2%	6%	3%	4%
Abdominal Pain	4%	3%	11%	1%	1%
Dyspepsia	2%	<1%	6%	0%	0%
Flatulence	2%	1%	4%	1%	1%
<b>General Disorders and Administration Site Conditions</b>					
Asthenia	4%	3%	9%	<1%	<1%
<b>Infections and Infestations</b>					
Bronchitis	0%	0%	2%	0%	<1%
<b>Investigations</b>					
Weight decreased	1%	<1%	2%	0%	<1%
<b>Metabolism and Nutrition Disorders</b>					
Anorexia	1%	<1%	2%	<1%	1%
<b>Musculoskeletal and Connective Tissue Disorders</b>					
Myalgia	1%	1%	2%	0%	0%
<b>Nervous System Disorders</b>					
Headache	2%	2%	6%	2%	2%
Paresthesia	1%	1%	2%	0%	0%
<b>Psychiatric Disorders</b>					
Insomnia	2%	1%	3%	1%	0%
Depression	1%	2%	0%	0%	0%
Libido decreased	<1%	<1%	2%	0%	<1%
<b>Skin and Subcutaneous Tissue Disorders</b>					
Rash	1%	2%	5%	<1%	1%

continued

Table 2. continued

	Study 863 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
	KALETRA 400/100 mg Twice Daily + d4T + 3TC (N = 326)	Nefinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)	KALETRA Twice Daily <sup>2</sup> + d4T + 3TC (N = 100)	KALETRA 800/200 mg Once Daily + TDF +FTC (N=333)	KALETRA 400/100 mg Twice Daily + TDF +FTC (N=331)
<b>Vascular Disorders</b>					
Vasodilation	0%	0%	3%	0%	0%

1 Includes adverse reactions of possible or probable relationship to study drug.  
2 Includes adverse reaction data from dose group I (200/100 mg twice daily [N = 16] and 400/100 mg twice daily [N = 16]) and dose group II (400/100 mg twice daily [N = 35] and 400/200 mg twice daily [N = 33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.  
Definitions: d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir Disoproxil Fumarate; FTC = Emtricitabine

Table 3. Percentage of Adult Patients with Selected Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

	Study 888 (48 Weeks)		Study 957 <sup>2</sup> and Study 765 <sup>2</sup> (84-144 Weeks)	Study 802 (48 Weeks)	
	KALETRA 400/100 mg Twice Daily + NVP + NRTIs (N = 148)	Investigator- selected protease inhibitor(s) + NVP + NRTIs (N = 140)	KALETRA Twice Daily + NNRTI + NRTIs (N = 127)	KALETRA 800/200 mg Once Daily +NRTIs (N=300)	KALETRA 400/100 mg Twice Daily + NRTIs (N=299)
<b>Gastrointestinal Disorders</b>					
Diarrhea	7%	9%	23%	14%	11%
Nausea	7%	16%	5%	3%	7%
Vomiting	4%	12%	2%	2%	3%
Abdominal Pain	2%	2%	4%	2%	<1%
Abdominal Pain Upper	N/A	N/A	N/A	1%	2%
Dyspepsia	1%	1%	2%	1%	<1%
Flatulence	1%	2%	2%	1%	1%
Dysphasia	2%	1%	0%	0%	0%
<b>General Disorders and Administration Site Conditions</b>					
Asthenia	3%	6%	9%	<1%	<1%
Pyrexia	2%	1%	2%	0%	<1%
Chills	2%	0%	0%	0%	0%
<b>Investigations</b>					
Weight decreased	0%	1%	3%	<1%	<1%
<b>Metabolism and Nutrition Disorders</b>					
Anorexia	1%	3%	0%	0%	1%
<b>Musculoskeletal and Connective Tissue Disorders</b>					
Myalgia	1%	1%	2%	0%	0%
<b>Nervous System Disorders</b>					
Headache	2%	3%	2%	<1%	0%
Paresthesia	0%	1%	2%	0%	0%
<b>Psychiatric Disorders</b>					
Depression	1%	2%	3%	<1%	0%
Insomnia	0%	2%	2%	0%	<1%
<b>Skin and Subcutaneous Tissue Disorders</b>					
Rash	2%	1%	2%	0%	0%
<b>Vascular Disorders</b>					
Hypertension	0%	0%	2%	0%	0%

1 Includes adverse reactions of possible or probable relationship to study drug.  
2 Includes adverse reaction data from patients receiving 400/100 mg twice daily (n = 29) or 533/133 mg twice daily (n = 28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.  
3 Includes adverse reaction data from patients receiving 400/100 mg twice daily (n = 36) or 400/200 mg twice daily (n = 34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.  
Definitions: NVP = Nevirapine; NRTI = Nucleoside Reverse Transcriptase Inhibitors; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitors

## Less Common Adverse Reactions

Treatment-emergent adverse reactions occurring in less than 2% of adult patients receiving KALETRA in the clinical trials supporting approval and of at least moderate intensity are listed below by system organ class.

**Blood and Lymphatic System Disorders** Anemia, leukopenia, lymphadenopathy, neutropenia, and splenomegaly.

**Cardiac Disorders** Angina pectoris, atrial fibrillation, atrioventricular block, myocardial infarction, palpitations, and tricuspid valve incompetence.

**Ear and Labyrinth Disorders** Hyperacusis, tinnitus, and vertigo.

**Endocrine Disorders** Cushing's syndrome and hypothyroidism.

**Eye Disorders** Eye disorder and visual disturbance.

**Gastrointestinal Disorders** Abdominal discomfort, abdominal distension, abdominal pain lower, constipation, duodenitis, dry mouth, enteritis, enterocolitis, enterocolitis hemorrhagic, eructation, esophagitis, fecal incontinence, gastric disorder, gastric ulcer, gastritis, gastroesophageal reflux disease, hemorrhoids, mouth ulceration, pancreatitis, periodontitis, rectal hemorrhage, stomach discomfort, and stomatitis.

**General Disorders and Administration Site Conditions** Chest pain, cyst, drug interaction, edema, edema peripheral, face edema, fatigue, hypertrophy, and malaise.

**Hepatobiliary Disorders** Cholangitis, cholecystitis, cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly, jaundice, and liver tenderness.

**Immune System Disorders** Drug hypersensitivity, hypersensitivity, and immune reconstitution syndrome.

**Infections and Infestations** Bacterial infection, bronchopneumonia, cellulitis, folliculitis, furuncle, gastroenteritis, influenza, otitis media, perineal abscess, pharyngitis, rhinitis, sialadenitis, sinusitis, and viral infection.

**Investigations** Drug level increased, glucose tolerance decreased, and weight increased.

**Metabolism and Nutrition Disorders** Decreased appetite, dehydration, diabetes mellitus, hypovitaminosis, increased appetite, lactic acidosis, lipomatosis, and obesity.

**Musculoskeletal and Connective Tissue Disorders** Arthralgia, arthropathy, back pain, muscular weakness, osteoarthritis, osteonecrosis, and pain in extremity.

**Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)** Benign neoplasm of skin, lipoma, and neoplasm.

**Nervous System Disorders** Agnesia, amnesia, ataxia, balance disorder, cerebral infarction, convulsion, dizziness, dysgeusia, dyskinesia, encephalopathy, extrapyramidal disorder, facial palsy, hypertension, migraine, neuropathy, neuropathy peripheral, somnolence, and tremor.

**Psychiatric Disorders** Abnormal dreams, affect lability, agitation, anxiety, apathy, confusional state, disorientation, mood swings, nervousness, and thinking abnormal.

**Renal and Urinary Disorders** Hematuria, nephritis, nephrolithiasis, renal disorder, urine abnormality, and urine odor abnormal.

**Reproductive System and Breast Disorders** Breast enlargement, ejaculation disorder, erectile dysfunction, gynecomastia, and menorrhagia.

**Respiratory, Thoracic and Mediastinal Disorders** Asthma, cough, dyspnea, and pulmonary edema.

**Skin and Subcutaneous Tissue Disorders** Acne, alopecia, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dry skin, eczema, hyperhidrosis, idiopathic capillaritis, nail disorder, pruritis, rash generalized, rash maculo-papular, seborrhea, skin discoloration, skin hypertrophy, skin striae, skin ulcer, and swelling face.

**Vascular Disorders** Deep vein thrombosis, orthostatic hypotension, thrombophlebitis, varicose vein, and vasculitis.

**Laboratory Abnormalities** The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 4 (treatment-naïve patients) and Table 5 (treatment-experienced patients).

Table 4. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

Variable	Limit <sup>1</sup>	Study 863 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
		KALETRA 400/100 mg Twice Daily + d4T +3TC (N = 326)	Nefinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)	KALETRA Twice Daily + d4T + 3TC (N = 100)	KALETRA Once Daily + TDF +FTC (N=333)	KALETRA Twice Daily + TDF +FTC (N=331)
<b>Chemistry</b>	<b>High</b>					
Glucose	> 250 mg/dL	2%	2%	4%	0%	<1%
Uric Acid	> 12 mg/dL	2%	2%	5%	<1%	1%
SGOT/AST <sup>2</sup>	> 180 U/L	2%	4%	10%	1%	2%
SGPT/ALT <sup>2</sup>	>215 U/L	4%	4%	11%	1%	1%
GGT	>300 U/L	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	4%	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	3%	5%
<b>Chemistry</b>	<b>Low</b>					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	2%	2%
<b>Hematology</b>	<b>Low</b>					
Neutrophils	<0.75 x 10 <sup>9</sup> /L	1%	3%	5%	2%	1%

1 ULN = upper limit of the normal range; N/A = Not Applicable.  
2 Criterion for Study 730 was >5x ULN (AST/ALT).

Table 5. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

Variable	Limit <sup>1</sup>	Study 888 (48 Weeks)		Study 957 <sup>2</sup> and Study 765 <sup>2</sup> (84-144 Weeks)	Study 802 (48 Weeks)	
		KALETRA 400/100 mg Twice Daily + NVP + NRTIs (N = 148)	Investigator- selected protease inhibitor(s) + NVP + NRTIs (N = 140)	KALETRA Twice Daily + NNRTI + NRTIs (N = 127)	KALETRA 800/200 mg Once Daily +NRTIs (N=300)	KALETRA 400/100 mg Twice Daily +NRTIs (N=299)
<b>Chemistry</b>	<b>High</b>					
Glucose	>250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST <sup>4</sup>	>180 U/L	5%	11%	8%	3%	2%
SGPT/ALT <sup>4</sup>	>215 U/L	6%	13%	10%	2%	2%
GGT	>300 U/L	N/A	N/A	29%	N/A	N/A
Total Cholesterol	>300 mg/dL	20%	21%	39%	6%	7%
Triglycerides	>750 mg/dL	25%	21%	36%	5%	6%
Amylase	>2 x ULN	4%	8%	8%	4%	4%
Lipase	>2 x ULN	N/A	N/A	N/A	4%	1%
Creatine Phosphokinase	>4 x ULN	N/A	N/A	N/A	4%	5%
<b>Chemistry</b>	<b>Low</b>					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%	1%	<1%
<b>Hematology</b>	<b>Low</b>					
Neutrophils	<0.75 x 10 <sup>9</sup> /L	1%	2%	4%	3%	4%
Hemoglobin	<80 g/L	1%	1%	1%	1%	2%

1 ULN = upper limit of the normal range; N/A = Not Applicable.  
2 Includes clinical laboratory data from patients receiving 400/100 mg twice daily (n = 29) or 533/133 mg twice daily (n = 28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.  
3 Includes clinical laboratory data from patients receiving 400/100 mg twice daily (n = 36) or 400/200 mg twice daily (n = 34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.  
4 Criterion for Study 802 was >5x ULN (AST/ALT).

**Pediatric Patients - Clinical Trials Experience** KALETRA oral solution dosed up to 300/75 mg/m<sup>2</sup> has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse reaction profile seen during Study 940 was similar to that for adult patients.

Dysgeusia (22%), vomiting (21%), and diarrhea (12%) were the most common adverse reactions of any severity reported in pediatric patients treated with combination therapy for up to 48 weeks in Study 940. A total of 8 patients experienced adverse reactions of moderate to severe intensity. The adverse reactions meeting these criteria and reported for the 8 subjects include: hypersensitivity (characterized by fever, rash and jaundice), pyrexia, viral infection, constipation, hepatomegaly, pancreatitis, vomiting, alanine aminotransferase increased, dry skin, rash, and dysgeusia. Rash was the only event of those listed that occurred in 2 or more subjects (N = 3).

KALETRA oral solution dosed at 300/75 mg/m<sup>2</sup> has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included decreased neutrophil count (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2). KALETRA oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg/m<sup>2</sup> (without concomitant NNRTI) and 480/120 mg/m<sup>2</sup> (with concomitant NNRTI) have been studied in 26 pediatric patients 7 to 18 years of age in Study 1038. Patients also had saquinavir mesylate added to their regimen at Week 4. Rash (12%), blood cholesterol abnormal (12%) and blood triglycerides abnormal (12%) were the only adverse reactions reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included rash (N=3), blood triglycerides abnormal (N=3), and electrocardiogram QT prolonged (N=2). Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities.

**Laboratory Abnormalities** The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 6.

**Table 6. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients in Study 940**

Variable	Limit <sup>1</sup>	KALETRA Twice Daily + RTIs (N = 100)
<b>Chemistry</b>	<b>High</b>	
Sodium	> 149 mEq/L	3%
Total Bilirubin	≥ 3.0 x ULN	3%
SGOT/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%
Total Cholesterol	> 300 mg/dL	3%
Amylase	> 2.5 x ULN	7% <sup>2</sup>
<b>Chemistry</b>	<b>Low</b>	
Sodium	< 130 mEq/L	3%
<b>Hematology</b>	<b>Low</b>	
Platelet Count	< 50 x 10 <sup>9</sup> /L	4%
Neutrophils	< 0.40 x 10 <sup>9</sup> /L	2%

1 ULN = upper limit of the normal range.  
2 Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

**Postmarketing Experience** The following adverse reactions have been reported during postmarketing use of KALETRA. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to KALETRA exposure.

**Body as a Whole** Redistribution/accumulation of body fat has been reported [see *Warnings and Precautions*].

**Cardiovascular** Bradycardia/arrhythmias. First-degree AV block, second-degree AV block, third-degree AV block, QTc interval prolongation, torsades (torsade) de pointes [see *Warnings and Precautions*].

**Skin and Appendages** Toxic epidermal necrolysis (TEN), Stevens Johnson Syndrome and erythema multiforme.

**DRUG INTERACTIONS**

See also *Contraindications, Warnings and Precautions*

**Potential for KALETRA to Affect Other Drugs** Lopinavir/ritonavir is an inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with KALETRA. Thus, co-administration of KALETRA with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 7.

Additionally, KALETRA induces glucuronidation.

**Potential For Other Drugs To Affect Lopinavir** Lopinavir/ritonavir is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce KALETRA's therapeutic effect. Although not observed in the KALETRA/ketoconazole drug interaction study, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

**Established and Other Potentially Significant Drug Interactions** Table 7 provides a listing of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

**Table 7. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
<b>HIV-1 Antiviral Agents</b>		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz, nevirapine	↓ lopinavir	KALETRA dose increase is recommended in all patients. Increasing the dose of KALETRA tablets to 500/125 mg (given as two 200/50 mg tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz resulted in similar lopinavir concentrations compared to KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz. Increasing the dose of KALETRA tablets to 600/150 mg (given as three 200/50 mg tablets) twice daily co-administered with efavirenz resulted in significantly higher lopinavir plasma concentrations compared to KALETRA tablets 400/100 mg twice daily without efavirenz. KALETRA should not be administered once daily in combination with efavirenz or nevirapine.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		KALETRA tablets can be administered simultaneously with didanosine without food. For KALETRA oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitor: abacavir, zidovudine	↓ abacavir ↓ zidovudine	KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.
HIV-1 Protease Inhibitor: amprenavir*	↑ amprenavir ↓ lopinavir	KALETRA should not be administered once daily in combination with amprenavir.
HIV-1 Protease Inhibitor: fosamprenavir/ritonavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse reactions has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: indinavir	↑ indinavir	Decrease indinavir dose to 600 mg twice daily, when co-administered with KALETRA 400/100 mg twice daily. KALETRA once daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	KALETRA should not be administered once daily in combination with nelfinavir.
HIV-1 Protease Inhibitor: ritonavir	↑ lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: saquinavir	↑ saquinavir	The saquinavir dose is 1000 mg twice daily, when co-administered with KALETRA 400/100 mg twice daily. KALETRA once daily has not been studied in combination with saquinavir.
HIV-1 Protease Inhibitor: tipranavir	↓ lopinavir AUC and C <sub>min</sub>	KALETRA should not be administered with tipranavir (500 mg twice daily) co-administered with ritonavir (200 mg twice daily).
HIV CCR5 – antagonist: maraviroc	↑ maraviroc	Concurrent administration of maraviroc with KALETRA will increase plasma levels of maraviroc. When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for Selzentry® (maraviroc).
<b>Other Agents</b>		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with KALETRA.
Anticancer Agents: vincristine, vinblastine, dasatinib, nilotinib	↑ anticancer agents	Concentrations of these drugs may be increased when co-administered with KALETRA resulting in the potential for increased adverse events usually associated with these anticancer agents. For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when KALETRA is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as KALETRA. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly and should be used with caution. KALETRA should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin. In addition, co-administration of phenytoin and KALETRA may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA.

continued

Table 7. continued

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
<i>Other Agents</i>		
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Concurrent administration of bupropion with KALETRA may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving KALETRA and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and KALETRA may increase concentrations of trazodone. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with $CL_{CR}$ 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with $CL_{CR}$ < 30 mL/min the dose of clarithromycin should be decreased by 75%.  No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole with KALETRA has not been studied. However, a study has been shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of KALETRA and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	↑ colchicine	Patients with renal or hepatic impairment should not be given colchicine with KALETRA.  <u>Treatment of gout flares-co-administration of colchicine in patients on KALETRA:</u>  0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.  <u>Prophylaxis of gout flares-co-administration of colchicine in patients on KALETRA:</u>  If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.  If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.  <u>Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on KALETRA:</u>  Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antimycobacterial: rifampin	↓ lopinavir	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg once daily, with KALETRA 800/200 mg twice daily or KALETRA 400/100 mg + ritonavir 300 mg twice daily. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a ≥ grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, KALETRA should not be given with orally administered midazolam [see <i>Contraindications</i> ]. If KALETRA is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
Calcium Channel Blockers, dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Contraceptive: ethinyl estradiol	↓ ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.
Corticosteroid: dexamethasone	↓ lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
disulfiram/metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Endothelin receptor antagonists: bosentan	↑ bosentan	<u>Co-administration of bosentan in patients on KALETRA:</u>  In patients who have been receiving KALETRA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.  <u>Co-administration of KALETRA in patients on bosentan:</u>  Discontinue use of bosentan at least 36 hours prior to initiation of KALETRA.  After at least 10 days following the initiation of KALETRA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Inhaled Steroid: fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and KALETRA may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Co-administration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect.
Long-acting beta-adrenoceptor agonist: salmeterol	↑ salmeterol	Concurrent administration of salmeterol and KALETRA is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesic: methadone fentanyl	↓ methadone ↑ fentanyl	Dosage of methadone may need to be increased when co-administered with KALETRA. Concentrations of fentanyl are expected to increase. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with KALETRA.

continued

Table 7. continued

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
<b>Other Agents</b>		
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	<p>Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection.</p> <p>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):</p> <p>Sildenafil (Revatio®) is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) because a safe and effective dose has not been established when used with KALETRA [see <i>Contraindications</i>].</p> <p>The following dose adjustments are recommended for use of tadalafil (Adcirca®) with KALETRA:</p> <p><b>Co-administration of ADCIRCA in patients on KALETRA:</b></p> <p>In patients receiving KALETRA for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><b>Co-administration of KALETRA in patients on ADCIRCA:</b></p> <p>Avoid use of ADCIRCA during the initiation of KALETRA. Stop ADCIRCA at least 24 hours prior to starting KALETRA. After at least one week following the initiation of KALETRA, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p>Use of PDE5 inhibitors for erectile dysfunction:</p> <p>It is recommended not to exceed the following doses:</p> <ul style="list-style-type: none"> <li>• Sildenafil: 25 mg every 48 hours</li> <li>• Tadalafil: 10 mg every 72 hours</li> <li>• Vardenafil: 2.5 mg every 72 hours</li> </ul> <p>Use with increased monitoring for adverse events.</p>

**Drugs with No Observed or Predicted Interactions with KALETRA** Drug interaction studies reveal no clinically significant interaction between KALETRA and desipramine (CYP2D6 probe), pravastatin, stavudine, lamivudine, omeprazole or ranitidine. Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy** Pregnancy Category C. No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred. No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

**Nursing Mothers**

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving KALETRA.

**Pediatric Use** The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. KALETRA once daily has not been evaluated in pediatric patients.

An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of with 300/75 mg/m<sup>2</sup> twice daily plus two NRTIs in HIV-infected infants ≥14 days and < 6 months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir AUC<sub>0-12</sub> than older children (6 months to 12 years of age), however, despite the lower lopinavir drug exposure observed, antiviral activity was demonstrated as reflected in the proportion of subjects who achieved HIV-RNA <400 copies/mL at Week 24 [see *Adverse Reactions*].

Safety and efficacy in pediatric patients > 6 months of age was demonstrated in a clinical trial in 100 patients. The clinical trial was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety, and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive and experienced pediatric patients ages 6 months to 12 years. Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m<sup>2</sup> oral solution twice daily regimen without nevirapine and the 300/75 mg/m<sup>2</sup> oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine) [see *Adverse Reactions*].

A prospective multicenter, open-label trial evaluated the pharmacokinetic profile, tolerability, safety and efficacy of high-dose KALETRA with or without concurrent NNRTI therapy (Group 1: 400/100 mg/m<sup>2</sup> twice daily + ≥ 2 NRTIs; Group 2: 480/120 mg/m<sup>2</sup> twice daily + ≥ 1 NRTI + 1 NNRTI) in children and adolescents ≥ 2 years to < 18 years of age who had failed prior therapy. Patients also had saquinavir mesylate added to their regimen. This strategy was intended to assess whether higher than approved doses of KALETRA could overcome protease inhibitor cross-resistance. High doses of KALETRA exhibited a safety profile similar to those observed in previous trials; changes in HIV-1 RNA were less than anticipated; three patients had HIV-1 RNA <400 copies/mL at Week 48. CD4+ cell count increases were noted in the eight patients who remained on treatment for 48 weeks [see *Adverse Reactions*].

**Geriatric Use** Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Hepatic Impairment** KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased [see *Warnings and Precautions*].

**OVERDOSAGE**

Overdoses with KALETRA oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of KALETRA oral solution nine days prior. However, a causal relationship between the overdose and the outcome could not be established. Healthcare professionals should be aware that KALETRA oral solution is highly concentrated and therefore, should pay special attention to accurate calculation of the dose of KALETRA, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children.

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with KALETRA is limited. Treatment of overdose with KALETRA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with KALETRA. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

**PATIENT COUNSELING INFORMATION**

See Medication Guide

**Information For Patients**

**Patients or parents of patients should be informed that:**

**General Information**

- They should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of KALETRA.
- They should inform their healthcare provider if their children's weight changes in order to make sure that the child's KALETRA dose is the correct one.
- They should take the prescribed dose of KALETRA as directed and to set up a daily routine in order to do so.
- KALETRA tablets may be taken with or without food. KALETRA oral solution should be taken with food to enhance absorption.

Sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

KALETRA is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV-1 to others through sexual contact, sharing needles, or being exposed to their blood. For their health and the health of others, it is important that they always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. They should also be advised to never re-use or share needles.

In addition to the above general counseling information, patients should be counseled about the important drug interactions, warnings, precautions, contraindications and adverse events associated with the use of Kaletra, as outlined in the Professional Brief Summary and Section 17 of the Full Prescribing Information.

Additional important information is also available for patients in the Medication Guide and Full Prescribing Information, which is available at kaletra.com or by calling Abbott Medical Information at 1-800-633-9110.

KALETRA Tablets, 200 mg lopinavir/50 mg ritonavir  
Manufactured by Abbott Pharmaceuticals PR Ltd., Barceloneta, PR 00617  
for Abbott Laboratories, North Chicago, IL 60064, U.S.A

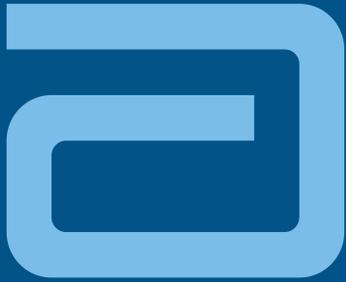
KALETRA Tablets, 100 mg lopinavir/25 mg ritonavir and KALETRA Oral Solution  
Abbott Laboratories, North Chicago, IL 60064, U.S.A.

Ref: 03-A387  
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Celebrating

**10**  
**YEARS**

of FDA Approval

**Do You Remember  
ABT-378?**



**September 2010** marks an important milestone for KALETRA: **10 years since its 2000 approval.**

Our commitment to patients and health care providers continues.

*Approved Since 2000*  
**KALETRA**<sup>®</sup>  
(lopinavir/ritonavir)

Please see Brief Summary of full Prescribing Information on adjacent pages.

