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Feature Article

Practice Tips

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ZIKA VIRUS

What New Jersey HIV and STD Providers Need to Know

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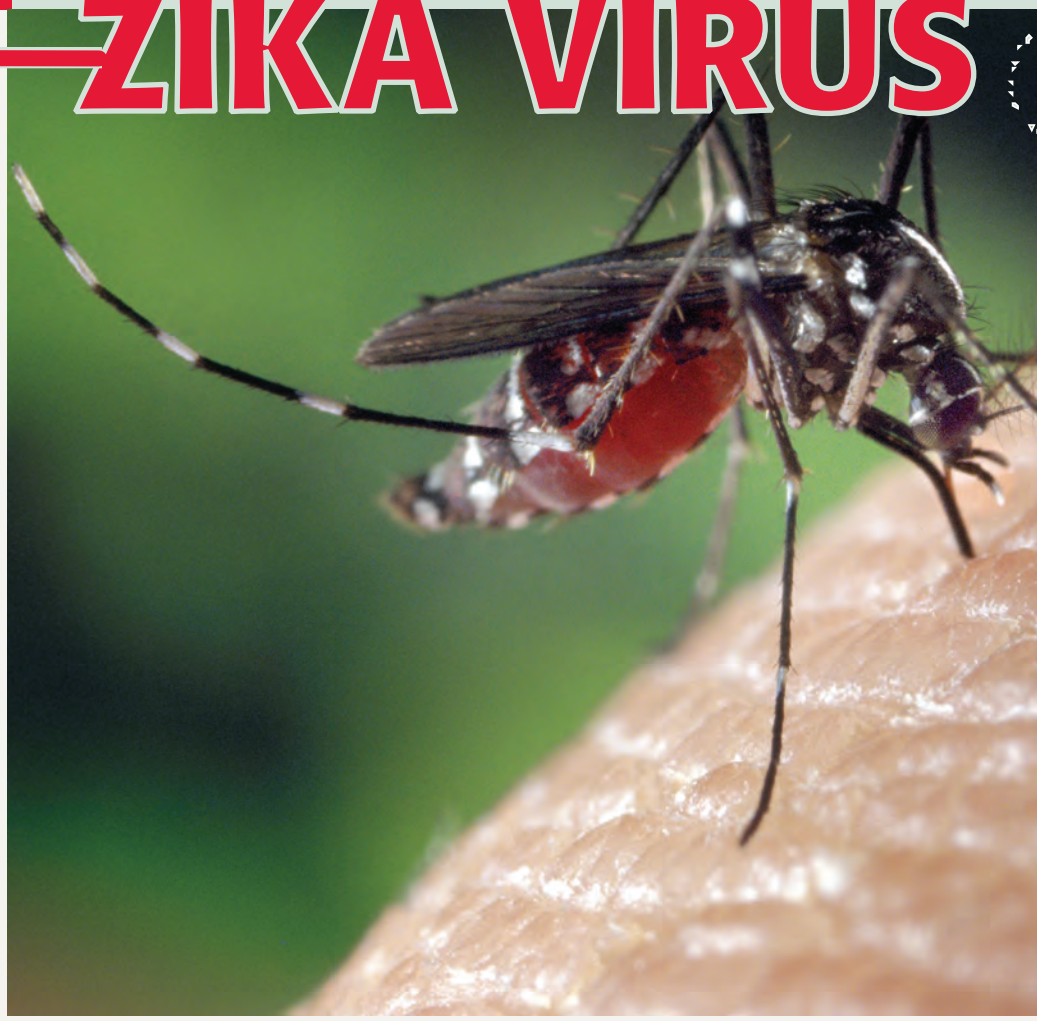

Aedes albopictus mosquito on human skin.

What is Zika?

Zika is a single-stranded ribonucleic acid (RNA) virus in the genus Flavivirus and is closely related to dengue, West Nile, Japanese encephalitis, and yellow fever viruses. Zika is primarily spread through the bite of an infected *Aedes* species mosquito. Zika can also be spread through sexual contact, from a pregnant woman to her fetus, and through blood transfusion and laboratory exposure. Since it was first identified in 1947, cases and outbreaks have occurred in tropical Africa, Southeast Asia and the Pacific Islands. In 2015, local transmission of Zika was identified for the first time in the Americas, in Brazil. As of September 23, 2016, 48 countries and territories in the Americas have reported ongoing local transmission of the virus.[1]

Zika in New Jersey

The Zika virus outbreak has caused international concern as the World Health Organization (WHO) declared the outbreak a public health emergency on February 1, 2016. While the United States (US) does not expect to see widespread outbreaks, and the risk of local transmission in New Jersey is low, combatting the virus and its associated health effects requires close surveillance, preparedness and prevention.

Almost 150 travel-related cases of Zika have been confirmed in 18 counties in New Jersey as of October 6, 2016.[2] Given New Jersey's diversity, with more than 20% of the population being foreign born, it is likely that additional travel-related cases will be identified. Although *Aedes aegypti*, the primary mosquito vector that transmits Zika virus, is not found in New Jersey, the risk of sexual transmission by infected travelers is present.

Symptoms and Complications

About one in five people infected with Zika develop symptoms and infection is usually mild. The most common symptoms are fever, rash, joint pain and red eyes. Other common symptoms include muscle pain and headache. Symptoms can last from several days to a week and usually begin 3-12 days after exposure. Once infected, a person is likely to be protected from future infections. Zika virus usually remains in the blood of an infected person for about a week.[1]

While it is rare for an individual with Zika to get seriously ill or die, evidence shows that some women infected with Zika during pregnancy may experience an adverse birth outcome or deliver a baby with birth defects. Congenital Zika syndrome is a recently recognized pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes microcephaly, intracranial calcifications or other brain abnormalities, or eye anomalies.[3]

Sexual Transmission of Zika

Zika can be passed from an infected person to his or her sex partners

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through vaginal, anal, and oral sex, as well as the sharing of sex toys. Sexual transmission is possible even if symptoms are not present or have ended, and even when an infected person never develops symptoms. Currently, it is known that Zika can remain in semen longer than in blood and other body fluids.[4,5] Additional studies are currently underway to determine how long Zika stays in semen and vaginal fluids, as well as the timeframe in which it can be passed between sex partners.[4]

Zika Prevention

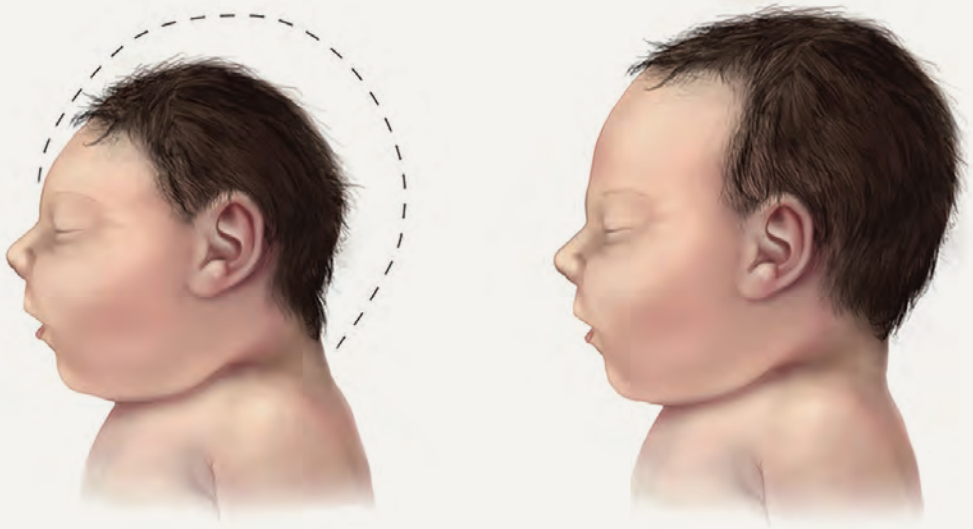
To prevent the spread of Zika through sexual contact, barrier methods (external or internal condoms and dental dams) should be used for all sexual activities, including vaginal, anal, and oral sex, as well as the sharing of sex toys. Abstaining from sexual contact also prevents Zika transmission to sex partners.

Individuals who have traveled to areas with ongoing Zika transmission* and their partners are advised to abstain from all sexual activity or use barrier methods for the following time periods[4]:

- At least **8 weeks** after a Zika diagnosis or start of symptoms if the traveling partner is female.
- At least **6 months** after Zika diagnosis or start of symptoms if the traveling partner is male.
- At least **8 weeks** after returning, if the traveling partner has no symptoms, regardless of sex or gender.

In addition, the Centers for Disease Control and Prevention (CDC) recommends that women wishing to conceive a child wait at least **8 weeks** after onset of symptoms or last possible exposure to Zika before trying to get pregnant. Men are advised to wait at least **6 months** after onset of symptoms or last possible exposure to Zika before trying to conceive a child with a partner.[4] Pregnant women whose sexual partner traveled to an area with ongoing transmission* are advised to use condoms or other barrier methods correctly every time they have vaginal, anal, or oral sex or not to have sex for the entire pregnancy.[4]

Zika prevention also includes avoiding mosquito bites by applying an Environmental Protection Agency (EPA)-registered insect repellent such as DEET (safe for use on pregnant women and children greater than two months of age); wearing long-sleeved shirts and pants when outdoors; removing standing water from bird-



The CDC illustration above depicts a baby with microcephaly (left) compared to a baby with a typical head size http://www.cdc.gov/ncbddd/birthdefects/images/microcephaly-comparison-500px.jpg

baths, pet dishes, flower pots, tires, wading pools and other containers where mosquitoes may breed; and, when indoors, using air conditioning or screens on windows and doors.[1]

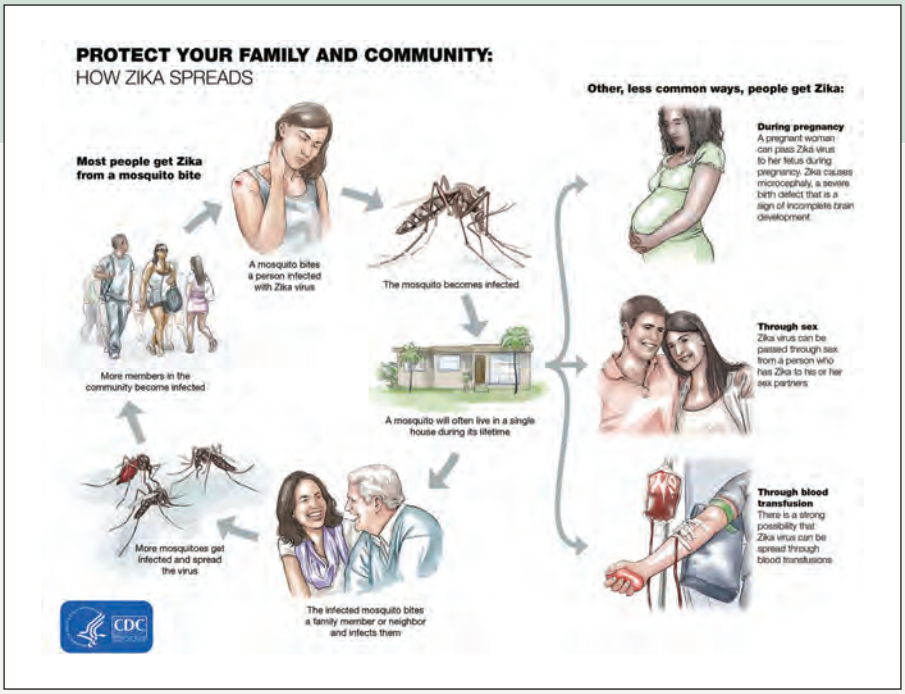
To protect the nation's blood supply, blood banks have been using a survey to screen donors, and individuals who traveled to areas with ongoing Zika transmission* are asked to defer from donating blood for 28 days. In addition, the Food and Drug Administration (FDA) recently recommended that all states and US territories begin screening individual units of donated whole blood and blood components with a blood screening test.[6]

*Areas with ongoing Zika transmission can be found at: http://www.cdc.gov/zika/geo/

Talking to Patients about Zika

To ensure efficient surveillance, assess risk of exposure and assist in preventing infections, it is important that clinicians take a thorough history and educate patients of the potential risks of infection and possible routes of transmission of Zika. Providers should advise pregnant women to avoid travel to areas where transmission is ongoing, and encourage couples seeking pregnancy to consider postponing their trip. In addition, clinicians should educate patients with recent travel history to abstain from sex or use condoms or dental dams for any sexual activity as outlined above.

The New Jersey Department of Health (NJDOH) asks that all providers stay up-to-date on the latest developments from the CDC, remember key disease prevention protocols, ask about travel history and sex partners, and stay alert for those with symptoms. It is important to regularly check the CDC Zika website (see Resources) as they continue to update guidance and travel advisories.



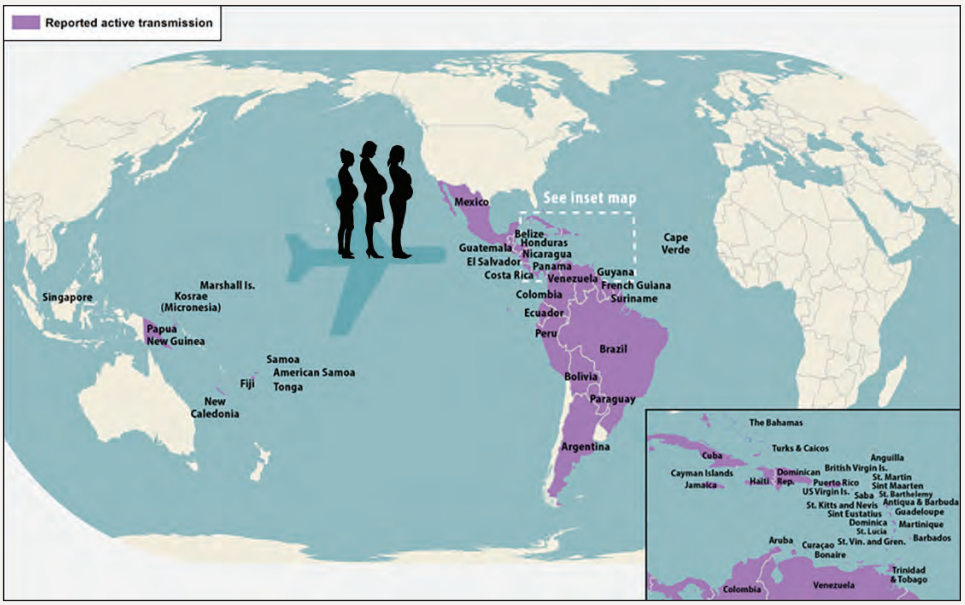
Zika Testing

CDC has recommended that pregnant women with possible exposure to Zika, including a history of travel to an area with Zika or possible sexual exposure, be tested for infection in consultation with their state or local health department. Testing can be offered 2-12 weeks after exposure. Infants born to mothers with possible Zika virus infection during pregnancy should be tested for Zika virus infection, regardless of maternal Zika virus test results.[7]

In non-pregnant persons, CDC recommends testing any individual with symptoms of Zika and recent exposure to the virus, including travel to areas with ongoing Zika transmission or possible sexual exposure.[6]

Testing bodily fluids (blood, semen, vaginal fluids, or urine) to determine how likely a person is to pass on Zika through sex is not recommended at this time, as currently available tests are limited in scope and may not accurately identify the presence of the Zika virus or a person's risk of passing it on.[6]

The NJDOH Public Health and Environmental Laboratories (PHEL) offers Zika testing; the criteria for testing can



Countries and territories with travel notices reporting active mosquito transmission of Zika virus.
http://www.cdc.gov/zika/geo/active-countries.html

be found on the NJDOH website at http://www.nj.gov/health/cd/zika/techinfo.shtml. Although Zika testing is also available through commercial laboratories, these tests do not rule out Zika infection and should not be used as the sole basis for patient management decisions. As such, the NJDOH recommends providers continue to use the PHEL in persons who meet the criteria for Zika testing at NJDOH. Providers seeking testing at PHEL must get specimens approved by their local health department prior to shipping to NJDOH. Contact information for local health departments can be found at www.localheatlh.nj.gov/.

Treatment

To date, there are no vaccines or medical treatments available to stop the progression of the infection. Treatment for Zika is generally supportive and can include rest, fluids, and use of pain relievers and fever reducers. Since dengue presents similarly to Zika, non-steroidal anti-inflammatories (eg, ibuprofen and aspirin) should be avoided until dengue is ruled out because taking these medications can put dengue patients at risk for hemorrhagic complications.

Zika Reporting

As per New Jersey Administrative Code (N.J.A.C. 8:57), healthcare providers are required to report cases of Zika virus within 24 hours of diagnosis to the local health department where the patient resides. Contact information for local health departments can be found at www.localheatlh.nj.gov/. Timely reporting is critical to effective disease surveillance, and also allows public health to connect healthcare partners and their patients to important resources, such as the US Zika Pregnancy Registry for infected pregnant women and Early Intervention Services (EIS) for potentially impacted infants and children.

New Jersey Provider Resources

- **NJ Zika Call Center:** The NJDOH and New Jersey Poison Information and Education System (NJPIES) operate a Zika call center for health care professionals as well as the general public. The call center is open 24 hours a day and can answer questions in any language. The telephone number is **800-962-1253**.
- **NJDOH Website:** The NJDOH posts information about Zika for providers and the general public: http://nj.gov/health/cd/zika.
- **NJDOH Social Media:** Twitter.com/NJDeptofHealth; Facebook.com/NJDeptofHealth
- **CDC Website:** CDC provides ongoing and updated information about Zika including travel advisories and guidance. http://www.cdc.gov/zika/index.html.
- **NJDOH Maternal Child Health (MCH) Provider Resource List:** The MCH Provider List is available to assist providers in identifying programs and services for their patients. This catalog contains existing MCH resources that can be used to address some of the needs of patients with the Zika virus as deemed appropriate. http://www.nj.gov/health/fhs/professional/documents/mch_provider_resource_list.pdf
- **NJDOH Family Health Services Hotline:** For general information on a range of helpful resources such as prenatal care, Federally Qualified Health Centers, Women, Infants and Children (WIC) or Special Child Early Intervention Services (SCHEIS), call the Family Health Services 24/7 Helpline at **1-800-328-3838**.
- **Zika Pregnancy Registry:** CDC has information and fact sheets about the Zika Pregnancy Registry at http://www.cdc.gov/zika/hc-providers/registry.html. For questions about the registry please e-mail ZikaPregnancy@cdc.gov or call **770-488-7100**. Print resources are available at http://www.cdc.gov/zika/fs-posters/index.html. ❖

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Addressing the Opioid Crisis in New Jersey: Bridging Public Health and Law Enforcement Efforts

Arturo Brito, MD, MPH, Deputy Commissioner, New Jersey Department of Health (DOH); **Captain Juan Colon, BA,** Bureau Chief, New Jersey State Police, Drug Monitoring Initiative; **Tim Seplaki, BS, NRP, CPM,** Data Manager & Analyst, Office of Emergency Medical Services, New Jersey DOH; **Dylan Wulderk**, MPA, Drug Policy Analyst, New York/New Jersey High Intensity Drug Trafficking Area (December 2015 – October 2016)

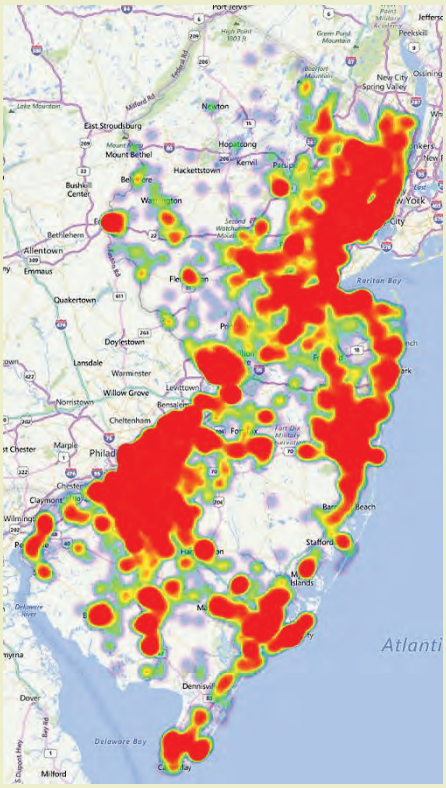
New Jersey, like most of the nation, is facing an ever-growing opioid crisis. Drug-related deaths are the number one cause of accidental deaths in New Jersey, with more than 2,600 lives lost to drugs in the state between 2013 and 2014. In 2014 alone, more than 700 drug-related deaths in the state involved heroin, and when prescription opioids, morphine, and fentanyl are included, the number of opioid-related deaths rises even higher.[1]

State Actions

In the face of this crisis, New Jersey Governor Chris Christie has responded with key actions to prevent overdoses from occurring. In July 2015, for instance, he signed a bill expanding the scope and strictness of the state's prescription monitoring program. This law requires all prescribers and pharmacists practicing in New Jersey to register for access to the New Jersey Prescription Monitoring Program (NJPMP) and mandates prescribers to check the NJPMP when patients return for refills on opioid medication. The intent is to limit access to unnecessary prescription opioids and help providers identify individuals potentially suffering from an opioid use disorder and provide interventions. Two other noteworthy Governor actions include the signing of the Overdose Prevention Act (OPA) in May 2013 and, through Executive Order, establishing the Facing Addiction Task Force (Task Force) in October 2014. The OPA provides immunity from arrest for persons seeking immediate medical assistance during a drug overdose. The Task Force is a twelve-member team with leadership from within and outside of government working together to define treatment and prevention efforts that address drug addiction. The State Health Commissioner is on the Task Force.

In March 2014, the Health Commissioner expanded the scope of practice for Emergency Medical Technicians (EMTs) to include the administration of naloxone in cases of life-threatening opioid overdoses with the Governor establishing a similar statewide program to train and equip police officers to administer the antidote in June 2014. Up until this date, only Advanced Life Support (ALS) agencies, staffed by Mobile Intensive Care paramedics and nurses, were able to administer naloxone. Between March 1, 2014 and October 12, 2016, ALS agencies reported 11,252 naloxone administrations in New Jersey. As of October 12, 2016, 311 Emergency Medical Services (EMS) Basic Life Support (BLS) agencies registered, providing 2,994 naloxone administrations, and law enforcement officers had provided 1,929 naloxone administrations.[2]

Other state agencies have also taken significant action to address the opioid crisis. The Department of Human Services, Division of Mental Health and Addiction Services, released two separate Request for Proposals in June 2015 to implement the Opioid Overdose Prevention Program (OOPP) and the Opioid Overdose Recovery Program (OORP). The OOPP established a prevention program comprised of education, outreach to at-risk individuals, collaboration with interested stakeholders, and distribution of naloxone rescue kits. Meanwhile, the OORP established an evidenced-based recovery program; supporting individuals reversed from opioid overdoses and treated at hospital emergency departments through the use of recovery specialists and patient navigators to provide non-clinical assistance, recovery support, and appropriate referrals for assessment and substance use disorder treatment. Both programs were expanded soon after their inception, with the OORP increasing its service from six to 11 counties and the OOPP expanding its reach from Central New Jersey to the Northern and Southern regions, as well.



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Governor Chris Christie announces New Jersey and New York have joined forces in the national fight against heroin and opioid addiction by sharing data to track prescription sales of narcotic painkillers and other drugs that often lead to addiction while at Englewood Hospital and Medical Center in Englewood, N.J. on Tuesday, April 26, 2016. (Governor's Office/Tim Larsen)

Data Sharing Between Health and Law Enforcement

Numerous other examples of state actions taken to minimize morbidity and mortality related to opioids exist. The remainder of this article will however focus on a specific collaboration between the New Jersey DOH and State Police (NJSP), within the Department of Law and Public Safety.

The National Governor's Association has identified the importance of using public health and law enforcement data to monitor trends and strengthen prevention efforts as a key health care strategy.[3] To that effect, the New Jersey Opioid Study Team (NJ OST) was established in September 2014. The goal of the NJ OST is to identify, use, and build upon existing data related to opioid use and misuse to drive state efforts in mitigating this public health problem. Specific objectives include: identification of existing data sources, analysis, and interpretation of information related to opioid use and misuse; identification of data gaps and development of strategies to address them, as appropriate; and sharing opioid-related data in meaningful and useful ways with key state agencies and other partners in order to decrease morbidity and mortality related to opioids.

The NJ OST is led by the DOH Deputy Commissioner, Public Health Services, and also includes representation from: DOH's Center for Health Statistics and Informatics and the Office of Emergency Medical Services; the Department of Human Services' Divisions of Medical Assistance and Health Services (Medicaid) and Mental Health and Addiction Services; Department of Children and Families; and, within the Department of Law and Public Safety, the Office of the State Medical Examiner and New Jersey State Police (NJSP).

Priority number one for the NJ OST is to develop an integrated data system which brings together existing data sets from different agencies. To that end, DOH and NJSP co-signed a Data Use Agreement (DUA) in 2014 allowing for the transfer of 12 key data points from the Office of Emergency Medical Services within DOH to NJSP. Data elements include: age, gender, race, ethnicity, date of incident, patient's home zip code, incident GPS location, possible injury, alcohol/drug use indicators, medication given, incident/patient disposition, and cause of injury. Privacy and confidentiality assurances were included. As per the agreement, the NJSP have analyzed DOH data through the Drug Monitoring Initiative (DMI) to geocode and map administrations, while overlaying naloxone data with heroin and other opioid seizures. DMI also collects naloxone administration data from law enforcement agencies statewide and combines this data with naloxone administration data from DOH to identify clusters within specific regions of the state.

Launched in 2013 and housed at the NJSP Regional Operations and Intelligence Center, DMI introduced a strategic shift by partnering law enforcement with diverse academic entities, research institutions, government agencies, and private organizations; establishing a common ground; and leveraging diverse subject matter expertise to fulfill the mission of combating the adverse impact of drugs on the state. The DMI established multijurisdictional drug incident information sharing and collaboration through comprehensive collection, analysis, and information sharing of drug seizures, criminal behavior, and healthcare-related services, such as naloxone administration. The result is a drug-intelligence capability that enables an understanding of drug-related activity statewide, bolstering decision-making for drug enforcement, prevention, treatment, and recovery. DMI helps to develop response plans, prioritize those responses, deploy resources, and predict future drug-related incidents.

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DMI uses several analytical methods such as "journey to overdose" to assist other entities in their drug prevention and enforcement efforts. The victim's city of residence and the location of the overdose are used to help determine if, for example, people from a rural area are traveling to urban areas where they are overdosing. To complement this effort, DOH uses electronic Patient Care Reporting (ePCR) technology to monitor overdose clusters by establishing "tripwires" that are triggered based on predetermined spatial and temporal parameters.

Once a naloxone administration "tripwire" is triggered, DMI alerts law enforcement and healthcare communities of the naloxone administration incidents and warns them about the potential for additional overdose incidents and surges within their jurisdictions. In turn, both law enforcement and healthcare professionals can better prepare for, respond to, and prevent overdose incidents within their jurisdictions, while also reaching out to their constituents to place them on heightened alert for potential overdoses resulting from heroin and opiates being sold and/or used within their community.

DOH has also begun educating EMTs about the importance of identifying and reporting if "stamps" (a specific image or symbol placed on the drug packaging by the drug seller to help individuals identify his/her specific product) are found on any "glassines" (the wax folder packaging containing the drug substance) at the scene. If a glassine heroin stamp name is associated with a suspected overdose, DMI can search the heroin stamp database to determine other locations where the same heroin stamp name has been encountered. The information is shared with law enforcement agencies, which can conduct controlled buys of heroin within the identified areas, with the intent to identify the source of the heroin causing the overdoses.

To increase the frequency of communication, DOH has also established an automated daily report containing aggregated data on EMS responses to suspected overdoses statewide. This report ensures that DMI receives information regarding overdose incidents that were not part of tripwire clusters. The aggregate overdose information is analyzed and data elements such as glassine stamp names and colors involved in overdoses are compared with the glassine heroin seizure data for commonalities. The results are published in DMI daily, weekly, and bimonthly reports for situational awareness.

Going Forward

DOH looks for further opportunities for collaboration with NJSP, other state agencies, and external partners to prevent opioid misuse through the effective use of data sharing. Recently, DOH was awarded a three-year, $2.1 million grant from the Centers for Disease Control and Prevention, to assist in improving the timeliness and effectiveness of the data exchange between agencies. This Data-Driven Prevention Initiative (DDPI) grant has two components: Planning and Data (P & D) and Prevention in Action (PIA).

The purpose of the P & D is to develop a state-wide, data-informed strategy to identify, implement, and drive effective programs and policies that enhance New Jersey's efforts to prevent and reduce opioid overuse, misuse, abuse, and overdose. By developing a strategic plan and data-sharing infrastructure, DOH and its partnering agencies will improve their ability to respond quickly and meaningfully to this ever-changing, ever-expanding public health crisis. Similar to the DMI's use of analytics such as "journey to overdose," DOH will be implementing a Prevention Pathways model through this grant component.

Prevention Pathways are evidence-informed, mitigation strategies that utilize a comprehensive approach to prevent, reduce, and eliminate drug misuse and abuse in New Jersey. Developed through collaborative and diverse partnerships, Prevention Pathways use key data points to form the State Data Set (currently a work in progress, but refers to a series of officially unconnected data sets housed within different departments; these data sets contain pieces of useful information and may overlap; the plan is to make these disperse data sets more unified) and are aggregated, analyzed, and mapped in order to target high-risk communities. Prevention Pathways recognize that all high-risk communities are not the same, and that they may be "supply communities," where drugs are often purchased, or "demand communities," where people with substance use disorders live and/or consume the drugs. With that in mind, each high-risk community is matched with a unique Prevention Pathway program, utilizing the entire spectrum of prevention to create effective interventions that weaken risk factors, strengthen protective factors, and reduce the incidence of drug misuse, abuse, and dependence.

The purpose of the PIA is to enhance the New Jersey Prescription Monitoring Program and related policies in order to maximize the state's ability to prevent and reduce opioid overuse, misuse, abuse, and overdose. This component will build on the P & D to identify and implement evidence-based interventions that strengthen the ability of opioid-focused programs and policies to achieve improved public health outcomes. This will help officials gain a truer picture of the opioid epidemic in New Jersey and further the State's efforts to reach its ultimate goal of reducing morbidity and mortality rates due to opioid overdoses. Ultimately, both grant components aim to reduce opioid-related overdoses and deaths. Strong partnerships between

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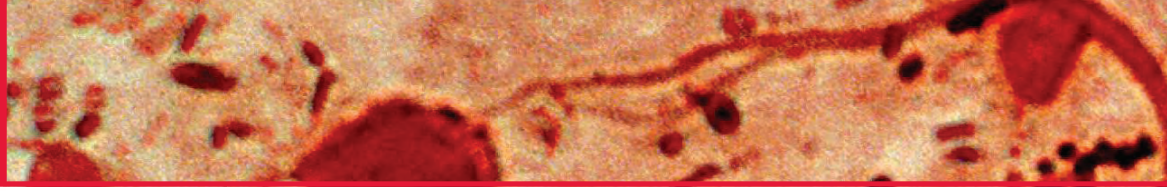

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State agencies and external agencies and the effective use of data to drive prevention efforts are critical to the success of these efforts. ❖

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Drug Resistant Gonorrhea

Patricia E. Mason, Senior Public Health Advisor, New Jersey Department of Health (DOH)/STD Program

- *Neisseria gonorrhoeae* ("gonorrhea") has developed varying degrees of resistance to antimicrobials used for treatment of gonorrhea over the past many years. Decreasing susceptibility to cefixime (an oral cephalosporin antibiotic) resulted in a recent change to the Centers for Disease Control (CDC) treatment guidelines, so that **dual therapy with ceftriaxone (an injectable cephalosporin) and azithromycin is now the ONLY CDC-recommended treatment regimen for gonorrhea**.[1,2]
- "Findings released from CDC's surveillance system for monitoring the threat of antibiotic-resistant gonorrhea show that the percentage of gonorrhea isolates with decreased susceptibility to azithromycin, an indicator of emerging resistance, increased more than 300 percent between 2013 and 2014 (from 0.6 percent to 2.5 percent of gonorrhea isolates). This is a distressing sign that the future of current treatment options may be in jeopardy and underscores the importance of the federal government's Combating Antibiotic Resistant Bacteria (CARB) Action Plan."[1]
- Total combined cases of **chlamydia, gonorrhea, and syphilis reported in 2015 reached the highest number ever recorded** by the Centers for Disease Control and Prevention (CDC).[3]
- Gonorrhea is the second most commonly reported sexually transmitted infection (STI) in the United States (US).[4]
- In 2015, 395,216 gonorrhea cases were reported in the US.[4]
- In the State of New Jersey, there were 6,636 reported cases in 2014; and, **in 2015, 7,228 cases were reported in New Jersey – a 9% increase**.[5]
- Populations that are adversely affected by gonorrhea include young men and women ages 15-34 (see Figure 1) and men who have sex with other men (MSM).[4]
- Screening all at-risk persons for genital and extra-genital site (pharyngeal and rectal) gonorrhea is essential.[2,6]

CDC Recommendations[7]

- **Take a sexual history.** This will help you know which STIs to test your patient for and at which anatomic sites.
- **Adhere to CDC's treatment recommendations** by always treating gonorrhea promptly with a combination of injectable ceftriaxone and oral azithromycin, including post-treatment testing to confirm cure when recommended (www.cdc.gov/std/treatment).
- **Follow key CDC screening recommendations**, including: Screen all sexually active women younger than 25 years, as well as older women with risk factors such as new or multiple sex partners, or a sex partner who has a STI; Screen sexually active MSM at anatomic sites of possible exposure at least annually.
- **Evaluate and treat all patients' sex partners** from the previous 60 days.
- **Obtain cultures** to test for decreased susceptibility from any patient with suspected or documented gonorrhea treatment failures.
- **Report any suspected treatment failure** to local or state public health officials within 24 hours, helping to ensure that any potential resistance is recognized early.

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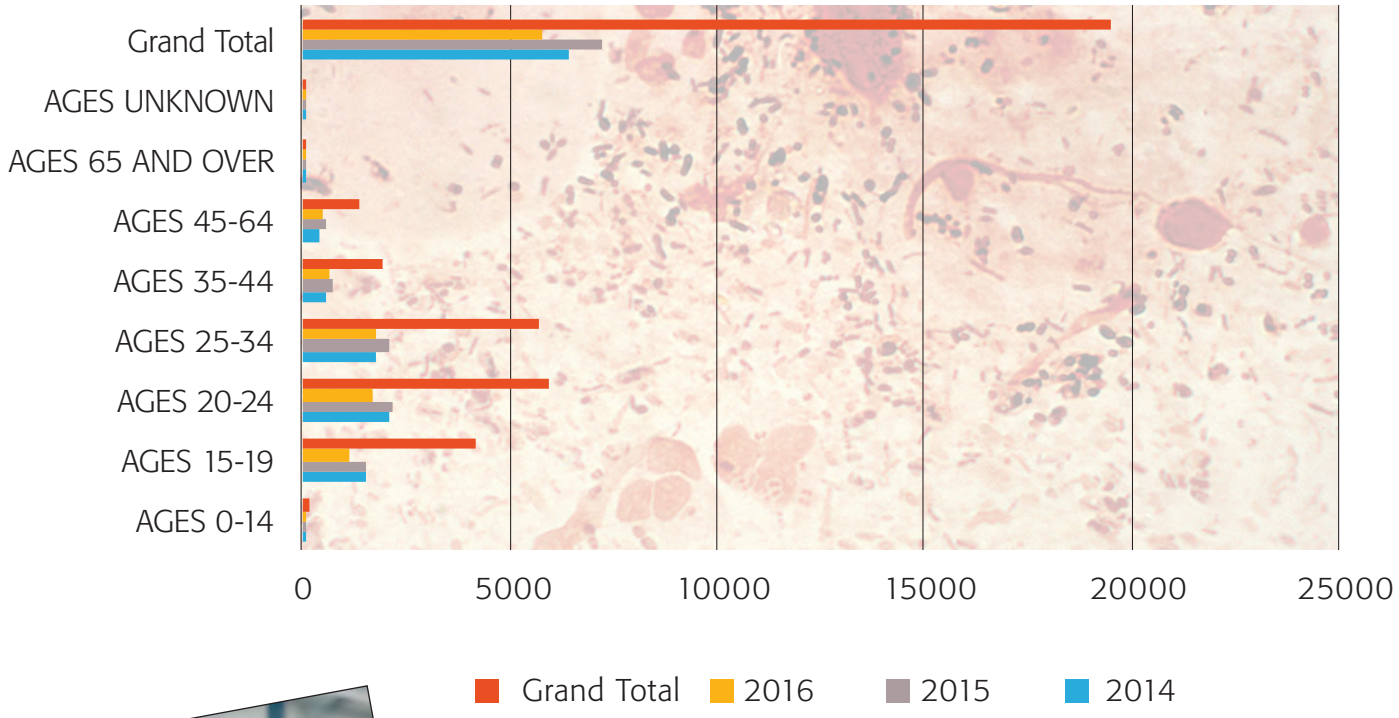
Figure 1: STD Prevalence in New Jersey 2014 - 2016*



*2016 rates reflects preliminary rates for January — September[8]

Pictured above: The growth of Neisseria gonorrhoeae colonies on New York City medium agar, a specialised and selective media for Gonococci. https://en.wikipedia.org/wiki/Neisseria_gonorrhoeae#/media/File:Neisseria_gonorrhoeae_Growth_on_New_York_City_Agar_Plate.jpg

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Health Insurance Premium Payment Program

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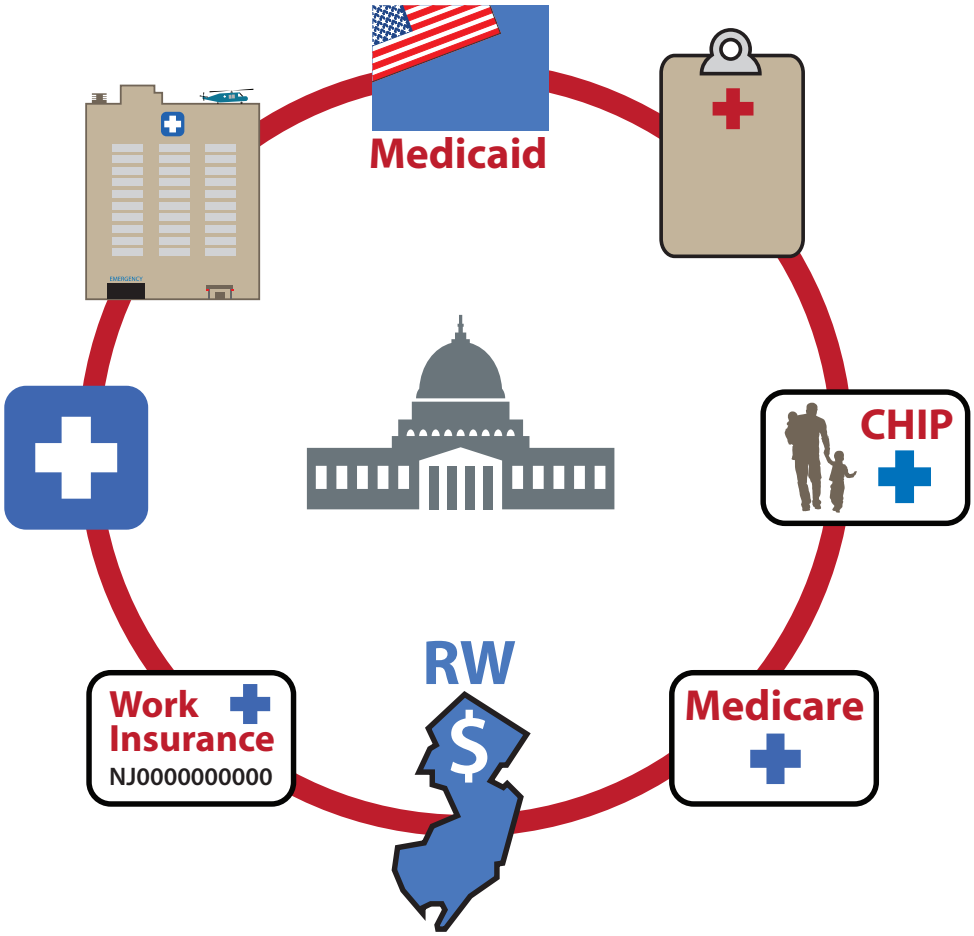
The Patient Protection and Affordable Care Act of 2010 (PPACA) provides significant benefits to all Americans particularly in states that have expanded Medicaid. In Medicaid expansion states, the percentage of uninsured residents decreased from 13% in 2013 to 9.3% in September 2014, as compared to non-Medicaid expansion states where the uninsured rate was 16% in 2013 and 13.5% in September 2014.[1] People living with HIV in New Jersey have the benefit of Medicaid Expansion and the Marketplace and on August 29, 2016, Governor Christie announced that 566,000 additional New Jerseyans have comprehensive health insurance coverage.

Assuring that all New Jersey residents living with HIV have continuous access to high quality health care and access to early initiation of antiretroviral therapy (ART) is essential for improving health outcomes, but also significantly reducing the risk for HIV transmission.

The Health Resources and Services Administration (HRSA) Ryan White HIV/AIDS Program plays an essential role in the evolving health care landscape by supporting and strengthening the safety net of HIV care and treatment services available to people living with HIV. The PPACA and other beneficial changes to the U.S. health care system help cities, states, and providers maximize their Ryan White HIV/AIDS Program resources, build a comprehensive system of care for low-income people living with HIV, and achieve the public health mandate of the Program.[2]



HRSA has authorized the use of Ryan White Part B Program funds to cover the cost of private health insurance premiums to assist eligible low–income clients in maintaining health insurance or receiving medical benefits under a health insurance or benefits program. HRSA policy states that to continue premium payments, states must ensure that grantees vigorously pursue all other health care coverage for which their clients may be eligible, e.g., Medicaid, CHIP, Medicare, state-funded HIV/AIDS programs, employer-sponsored health insurance coverage, and/or other private health insurance to extend finite Ryan White grant resources to new clients and/or needed services.

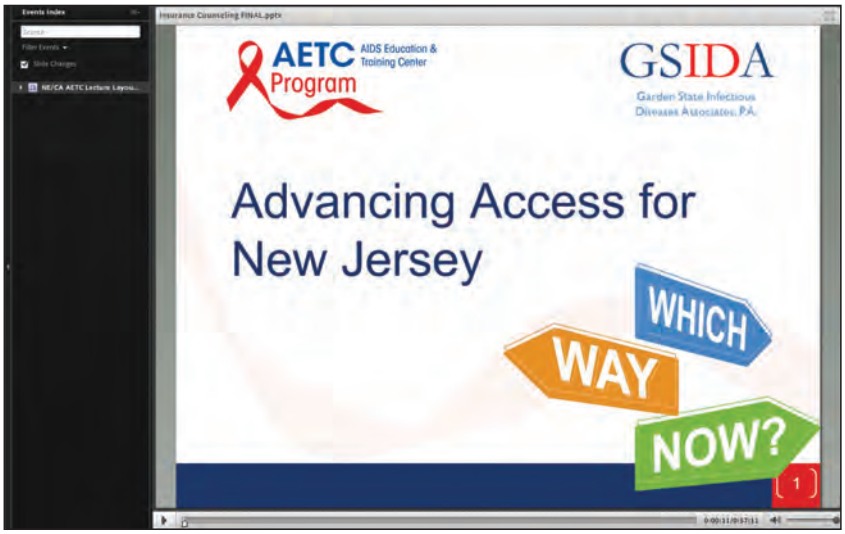
The Division of HIV, STD and TB Services (DHSTS) rolled out a Health Insurance Premium Payment (HIPP) program in December 2015 and is preparing for the 2016 Open Enrollment period set to run from November 1, 2016 to January 31, 2017. The HIPP program supports silver marketplace plans with prescription coverage that meet the HIV consumer's needs. The selected plan must include at least one drug in each class of core antiretroviral therapeutics from the HHS Clinical Guidelines for the Treatment of HIV/AIDS as well as appropriate primary care services.

Initial HIPP eligibility screening for applicants without insurance must be completed by a Certified Applications

continued on next page

Counselor (CAC) and submitted by a Medical Case Manager (MCM). DHSTS and AIDS Education and Training Center (AETC) of Southern New Jersey have collaborated on a health insurance instruction webinar for CACs and MCMs in preparation for the 2016 Open Enrollment period. The webinar will address benefits of having health insurance for the consumer, elements of selecting a plan, the penalty for not having health insurance, the New Jersey Marketplace Plans coverage and cost sharing options, how to apply and HIPP standards. The webinar will be archived on the AETC website and broadly marketed throughout New Jersey.

HIPP eligibility requires the applicant to be active in the AIDS Drug Distribution Program (ADDP). This will ensure that all Ryan White eligibility standards are met regarding diagnosis, residence and income. Individuals with household incomes of 139% to 500% of the Federal Poverty Level (FPL) are eligible for HIPP. Applicants falling between 139% and 400% of the FPL must apply for an Advance Tax Credit and have 100% of that credit applied to their monthly premium. The Advance Tax Credit is determined by the applicant's projection of annual income that must be adjusted on their tax return. Overstating or understating income may result in a tax refund or tax liability, either way the HIPP tax reconciliation policy must be followed by the Medical Case Manager. In addition, applicants with FPL of 401–500%: are eligible for out-of-market Silver Plans through private vendors, the premium cost may not exceed $900 per month. Clients with household income of 0–138% of FPL are eligible for Medicaid Expansion. NJFamilyCare is administered the Medicaid program. A downloadable online application can be found at http://www.njfamilycare.org/need_help.aspx along with a list of Medicaid Assisters. ❖



Additional helpful resources include:

Advancing Access to Health Insurance in NJ:

Introduction of health insurance premium payment pilot project (HIPP)

Health Insurance Enrollment:

https://careacttarget.org/library/supporting-health-coverage-enrollment-ryan-white-hivaids-program-clients

Health Literacy:

https://careacttarget.org/library/health-literacy-health-insurance-literacy-helping-consumers-access-care-and-use-coverage

Best Practice: Enrollment, engagement, and retention:

https://careacttarget.org/library/best-practices-engage-enroll-and-retain-ryan-white-hivaids-program-clients-health-coverage ❖

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PRACTICE TRANSFORMATION
and the AIDS Education and Training Center (AETC) Program:
What is it all about?

Andrea Norberg, MS, RN, Executive Director François-Xavier Bagnoud Center Rutgers School of Nursing, Principal Investigator AIDS Education and Training Center National Coordinating Resource Center

Practice transformation (PT) refers to a process of change in the organization and delivery of primary care to advance quality improvement, patient-centered care, and characteristics of high performing primary care. The AETC Program will implement projects to support and facilitate PT in selected clinics throughout the U.S. in order to improve patient outcomes along the HIV Care Continuum by integrating principles of the patient-centered medical home model and integrated HIV care and behavioral health services.[1] The PT process intends to increase the size and strength of the HIV clinical workforce and to improve outcomes along the HIV Care Continuum. The goal of PT is to work with selected Ryan White Part A or B clinics and non-Ryan White funded community health centers to build capacity to provide quality, comprehensive care and treatment to PLWH as evidenced by progress along the HIV Care Continuum.[2]

Practice transformation involves goal-setting, leadership and organizational development, practice facilitation, workflow analysis and changes, quality improvement and outcomes measurement, and adapting organizational tools and processes to support advances in models of team-based care. The AETC Program will provide practice facilitation or coaching to support these transformation efforts.[1]

Each regional AETC is expected to monitor and demonstrate progress towards the stated goals for each participating clinical site. The regional AETCs will contribute to a national evaluation of the PT projects, led by the AETC National Evaluation Center at University of California, San Francisco. In addition, The AETC National Coordinating Resource Center (NCRC) at the François-Xavier Bagnoud Center, Rutgers School of Nursing leads a national community of learning for regional PT Coordinators and Coaches to share lessons learned and to provide learning opportunities that improve facilitation and coaching skills.

The goal of the Northeast/Caribbean AETC, one of eight regional AETCs, PT Project is to facilitate the provision of high quality comprehensive care and

treatment of PLWH by transforming clinical practice in alignment with the goals of the National HIV/AIDS Strategy and as measured by progress along the HIV Care Continuum. The model employs a comprehensive multimodal longitudinal training approach for each participating site. Nine clinical sites have been identified for participation, representing a diverse group of care providers from all over the region. These clinics were chosen based on the high need of the populations served and the ability of the project to impact access to high quality clinical care. Two of these sites are in New Jersey.

The Northeast/Caribbean AETC partnered with the Millard Fillmore College Practice Facilitator Certificate Program at the University at Buffalo to train coaches to work with each site. This program has been highlighted by the USDHHS Agency for Healthcare Research and Quality as an exemplary primary care practice facilitation training program. The trained coaches are the primary resource for the region's PT program. Since PT is highly impacted by state, local and regional policies, the coaches' knowledge of their communities will greatly enhance their ability to facilitate practice change.

Each coach develops a longitudinal relationship with their PT site that includes in-depth need assessments and meetings with interdisciplinary teams of health care providers and clinic leadership on a regular basis. Each clinic has appointed a point person for the project. The coach is responsible for coordinating technical assistance (TA) and training requests, maintaining ongoing communication, and facilitating data collection to evaluate outcomes along the Continuum.

Given the importance of integrated care in the patient-centered medical home model, the PT program incorporates behavioral and oral health care. This is particularly important given the impact that behavioral health has on the Continuum and the relationship between oral and systemic health. The integration of clinical HIV and behavioral health services has been shown to improve quality of life outcomes and overall physical and mental health. Research demonstrates that cross training of HIV and behavioral health capacity-building increases clinical knowledge and service provision among individual providers. An association between oral health and systemic health is widely accepted by the medical and dental communities. Oral health status affects a person's general health and overall well-being throughout the life cycle and most profoundly affects vulnerable populations, especially PLWH.

In year 1 of the 4 year project, the Northeast/Caribbean AETC focused on planning and strategizing the PT approach with the sites utilizing the principles of medical home, patient-centered care and integrated behavioral health services. Based on the findings of the needs assessments and discussions with key stakeholders at the clinic, core goals for each site were identified. They ranged from supporting the use of the EHR and development of user friendly reports to inform Continuum outcomes, introducing "patient empanelment", working on Continuum outcomes (including durable suppression and engagement), and the development of team-based care models. The coaches work with the clinic leadership and providers of each site to develop a TA and training plan, and with the assistance of internal and external experts implement the plan and measure impact on outcomes.

Go to the AETC NCRC to access the following PT Resources: associated websites, a review of the literature on practice transformation efforts, practice readiness assessment tools, tips for engaging leadership, quality improvement tools, practice facilitation resources and various newsletters and forums:

https://www.aidsetc.org/topic/practice-transformation ❖

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The Past, Present, and Future of HIV Medications

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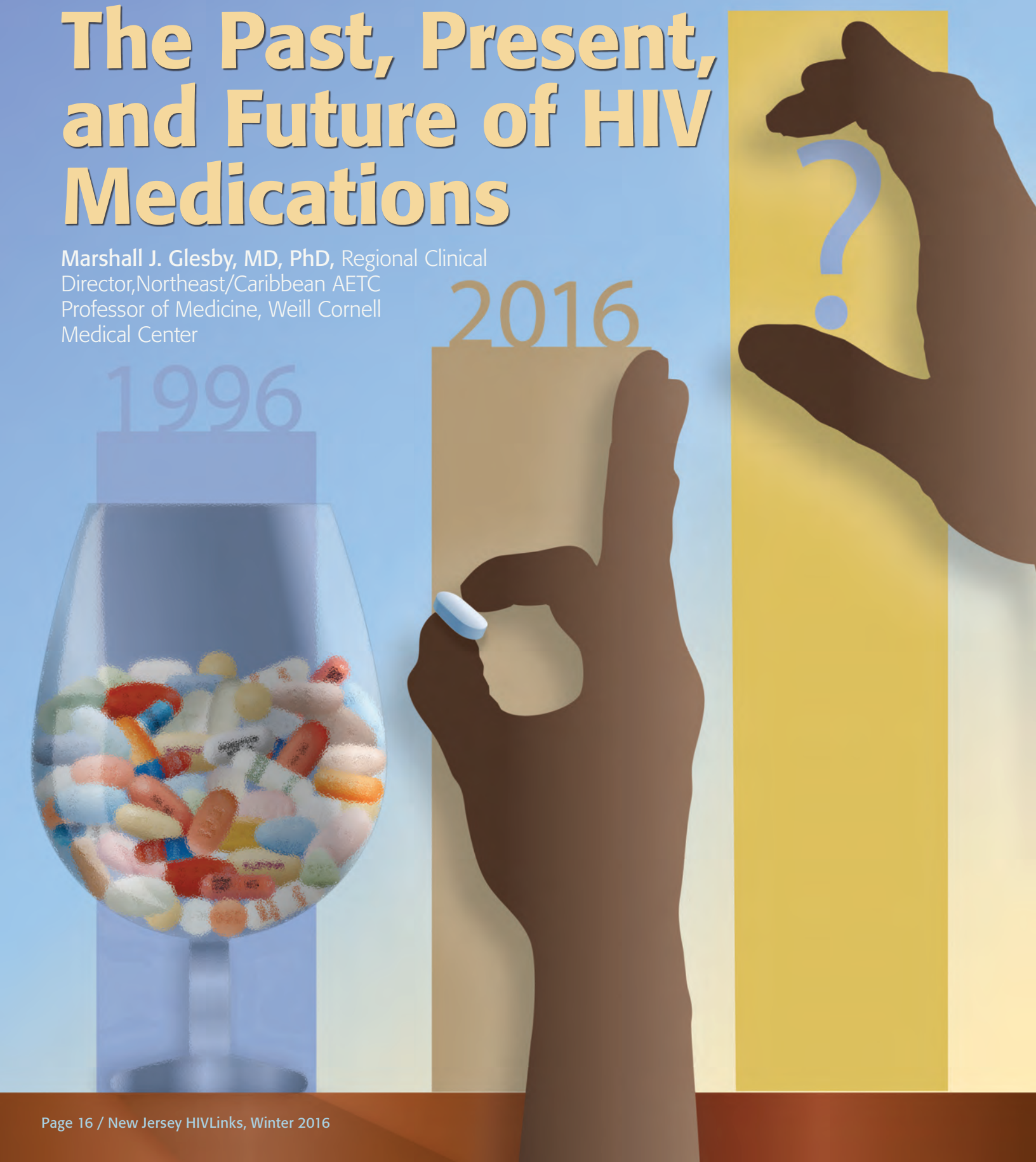

Recent modeling data suggest that the life expectancies of people living with HIV infection are beginning to approximate their peers who are uninfected, especially if antiretroviral therapy is started at a CD4 cell count above 500 cells/mm^3.[1] While many of our patients are unfortunately facing multiple co-morbidities, including aging-related syndromes, it is hard to deny the enormous progress that has been made as a result of developments in antiretroviral therapy. It is worth reflecting on where we have been, where we are now, and where we may be going with regard to HIV therapy.

The Past

In 1987, six years after the recognition of what was later termed AIDS, the FDA approved the first antiretroviral drug, zidovudine.[2] While initially hailed as a drug that improved survival, its limited benefits and significant toxicities, especially at the high dose used in that era, became apparent over time. The approvals of didanosine, zalcitabine, and stavudine in the early 1990s, yielded additional nucleoside reverse transcriptase inhibitor (NRTI) options for initial monotherapy or drug switches. Subsequent trials demonstrated the clinical benefits of adding a second NRTI to zidovudine, yet significant toxicities, such as peripheral neuropathy and pancreatitis, were all too common and efficacy was limited.

In 1995, the tide began to turn with the availability of the well-tolerated NRTI, lamivudine, and the first protease inhibitors (PIs), saquinavir, followed soon after by ritonavir and indinavir in 1996.[3] Nevirapine, the first non-nucleoside reverse transcriptase inhibitor (NNRT) was also approved in 1996, and the availability of HIV viral load testing improved our ability to monitor treatment responses. The new standard of care of two NRTIs plus a PI, led to dramatic reductions in mortality. Yet frequent dosing, high pill burdens, and significant toxicities—both short- and longer-term—posed major challenges. Over the ensuing years, newer drugs in existing classes, pharmacokinetic boosting of PIs initially with ritonavir, and co-formulations of two or more drugs led to improved tolerability and simpler dosing regimens. Newer classes of drugs, including an injectable fusion inhibitor (enfuvirtide in 2003), a CCR5 antagonist (maraviroc in 2007), and the first integrase inhibitor (raltegravir in 2007) provided life-saving options for patients with multidrug resistance who had exhausted most or all previously available antiretrovirals. Over the next decade, the availability of newer drugs within existing classes with more favorable side effect profiles or dosing requirements and a handful of single tablet combination regimens have provided clinicians and patients with multiple potent, well-tolerated, and easy to take initial regimens.

Strong data emerged in 2011 for the use of antiretroviral therapy to prevent transmission (so-called treatment as prevention) among heterosexual serodiscordant couples in the HIV Prevention Trials Network (HPTN) 052 trial.[4] These data, along with observational data supporting clinical benefits to initiating antiretroviral therapy at high CD4 cell counts, led major treatment guidelines to shift towards recommending antiretroviral therapy for all, regardless of CD4 cell count. Ultimately, in 2015, the Strategic Timing of Antiretroviral Therapy (START) trial conclusively demonstrated the benefits of initiating antiretroviral therapy at CD4 counts >500 cells/mm^3.[5]

The Present

In 2016, initial antiretroviral therapy for most adolescents and adults with HIV-1 infection consists of a single pill once a day that is generally well tolerated. In the current iteration of the US Department of Health and Human Services (DHHS) HIV-1-Infected Adults and Adolescents antiretroviral therapy guidelines, the recommended initial regimens are all integrase inhibitor based with the exception of one PI-based option of darunavir/ritonavir.[6] The FDA approval in 2016 of tenofovir alafenamide (TAF) as an alternative to the original pro-drug formulation, tenofovir disoproxil fumarate (TDF), has also expanded the population of patients who can safely receive tenofovir to include those with reduced creatinine clearance rates. Clinical trials have also demonstrated reduced adverse effects of TAF on bone mineral density and a lower risk of nephrotoxicity compared with TDF. Of the six currently recommended initial regimens, three are one pill once a day, two are two pills once a day, and one is one pill once a day plus a second pill twice a day. The latter regimen contains the integrase inhibitor raltegravir, which must currently be taken as one pill twice a day; of note, a two pill once a day for-

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mulation of raltegravir is under review at the FDA.

With these simpler, potent regimens, virologic suppression rates in many clinical settings are approaching the 90% rates seen in recent clinical trials. Yet some patients continue to struggle with adherence and a minority has multidrug resistant HIV with limited treatment options due to extensive prior treatment histories. Despite all of our advances, there continues to be a need for antiretroviral drug development and the study of newer strategies so that all HIV-infected patients in resource rich and resource limited settings may reap the benefits of therapy.

The Future

Ongoing research provides a glimpse of what the future may hold in the area of antiretroviral therapy. Investigators are studying several approaches to simplify the traditional three drug (excluding pharmacokinetic booster drugs) regimens. For example, preliminary data from the PADDLE trial led by Dr. Pedro Cahn in Argentina suggest that a two-drug regimen of dolutegravir plus lamivudine holds promise as an initial regimen.[7] While very high rates of virologic suppression were seen in this small study, we await more definitive data from a study of the same regimen by the AIDS Clinical Trials Group (ACTG) that includes patients with high baseline viral loads. This potent, well-tolerated two drug combination has the potential for co-formulation as a single tablet regimen.

Others are studying novel injectable drugs to maintain virologic suppression, such as the monoclonal antibody that targets CCR5, PRO140, given as a weekly subcutaneous injection. Similarly, infusions of so-called broadly neutralizing HIV antibodies, namely potent antibodies that can neutralize multiple strains of HIV, are also under study as a potential approach to maintaining virologic suppression off of traditional antiretroviral therapy.

The initial data on long-acting antiretroviral regimens appears promising and could eventually obviate the need for daily pill taking. The most mature of these data are for long-acting rilpivirine, a parenteral formulation of an existing NNRTI, and cabotegravir, an investigational integrase inhibitor that is an analogue of the FDA-approved dolutegravir. In the current generation of clinical trials, and perhaps for the foreseeable future, these long-acting medications are initially given in short-acting oral forms so that they can be stopped and wash out of the body in the event of significant short-term toxicities, such as rash or hypersensitivity. In the LATTE-2 trial, for example, participants received "induction" therapy with oral cabotegravir plus abacavir/lamivudine and later added oral rilpivirine to achieve virologic suppression prior to being randomly assigned to maintenance therapy with intramuscular injections of cabotegravir and long-acting rilpivirine every four or eight weeks (versus the control group of oral cabotegravir and abacavir/lamivudine). Week 48 data from this ongoing trial were presented at the 2016 International AIDS Society (IAS) Conference and showed comparable rates of virologic suppression across the study arms.[8] While mild injection site reactions and some systemic symptoms were seen commonly in patients assigned to the injectable medications, patients rated their satisfaction with the regimens as high on average. While promising, this approach may not be a panacea. The patient population that has the greatest need for therapeutic approaches that obviate the need for daily pill-taking—those with existing adherence challenges—would still need to have close follow-up with periodic injections and laboratory monitoring. The long half-lives of these novel antiretrovirals could readily lead to resistance if patients discontinue follow-up prematurely.

Of note, long-acting rilpivirine is being studied for pre-exposure prophylaxis (PrEP) as is injectable cabotegravir, the latter being compared to the standard of care regimen of tenofovir disoproxil fumarate/emtricitabine in a large randomized trial being conducted by the HPTN (enrolling at the Clinical Research Center at Rutgers University in Newark and multiple sites in New York City). Novel formulations of existing types of antiretrovirals are also in pre-clinical development, including subdermal implants (similar to what is used for contraception) and patches.

For the diminishing number of HIV-infected patients who have limited treatment options, there are a few new classes of antiretrovirals in development. Maturation inhibitors act at the viral maturation step, inhibiting cleavage of the HIV structural protein gag and preventing the development of an infective viral particle. BMS-955176 is the maturation inhibitor that is furthest along in clinical development; under study in treatment experienced patients in combination with atazanavir/ritonavir and dolutegravir.[9] Other drugs are in development to target the step of the viral lifecycle in which HIV binds to the CD4 receptor. These include the orally administered small molecule inhibitor, BMS-663068, which binds to gp120 of HIV and prevents its binding to CD4. This investigational drug is in phase III development. Ibalizumab is an investigational monoclonal antibody that inhibits the HIV-CD4 interaction by binding to CD4 on host cells. It is presently in phase III development in combination with optimized background regimens in highly treatment-experienced patients.

There are also investigational drugs in development that fit within existing classes, such as the NNRTI doravirine. Development of some of these drugs is challenging in the current era since there usually must be some advantage or niche for a new drug for it to be marketable. An extensive review of other drugs in development is beyond the scope of this article.

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Lastly, novel combinations of several of the aforementioned investigational drugs and monoclonal antibodies could result in maintenance therapy consisting of infrequent injections. For example, ACTG investigators plan to study long-acting cabotegravir plus VRC01LS, a broadly neutralizing antibody, as an approach to maintain virologic suppression.

Conclusions

While many people living with HIV infection in resource rich settings like the U.S. are virologically suppressed, there remains a need to develop both simple, well-tolerated antiretroviral regimens that will obviate the need for rigorous adherence and newer classes of drugs to help the minority of patients with multidrug resistance and limited treatment options. Given the tremendous progress made over the past three decades, ongoing and future research will undoubtedly yield new options for both HIV treatment and prevention. ❖

references on page 14

Recommended and Alternative Antiretroviral Regimen Options for Treatment-Naive Patients[6]

Recommended Regimen Options:
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxic profiles, and ease of use.

INSTI plus 2-NRTI Regimen:
- DTG/ABC/3TC[a] **(AI)** — if HLA-B*5701 negative
- DTG plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)**
- EVG/c/TAF/FTC **(AI)** or EVG/c/TDF/FTC **(AI)**

Boosted PI plus 2 NRTIs:
- DRV/r plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)**

Alternative Regimen Options:
Alternative regimens are effective and tolerable, but have potential disadvantages when compared with the Recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. **However, an Alternative regimen may be the preferred regimen for some patients.**

NNRTI plus 2 NRTIs:
- EFV/TDF/FTC[a] **(BI)**
- EFV plus TAF/FTC[b] **(BII)**
- RPV/TDF/FTC[a] **(BI)** or RPV/TAF/FTC[b] **(BII) – if HI RNA<100,000 copies/mL and CD4>200 cells/mm³**

Boosted PI plus 2 NRTIs:
- (ATV/c or ATV/r) plus either TDF/FTC[a] **(BI)** or TAF/FTC[b] **(BII)**
- DRV/c **(BIII)** or DRV/r **(BII)** plus ABC/3TC[a] — if HLA-B*5701 negative
- DRV/c plus either TDF/FTC[a] **(BII)** or TAF/FTC[b] **(BII)**

a. 3TC may be substituted for FTC, or vice versa, if a non-fixed dose NRTI combination is desired.

b. The evidence supporting this regimen is based on relative bioavailability data coupled with data from randomized, controlled switch trials demonstrating the safety and efficacy of TAF-containing regimens.

Note: The following are available as coformulated products: ABC/3TC, ATV/c, DRV/c, DTG/ABC/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, LPV/r, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, and TDF/FTC.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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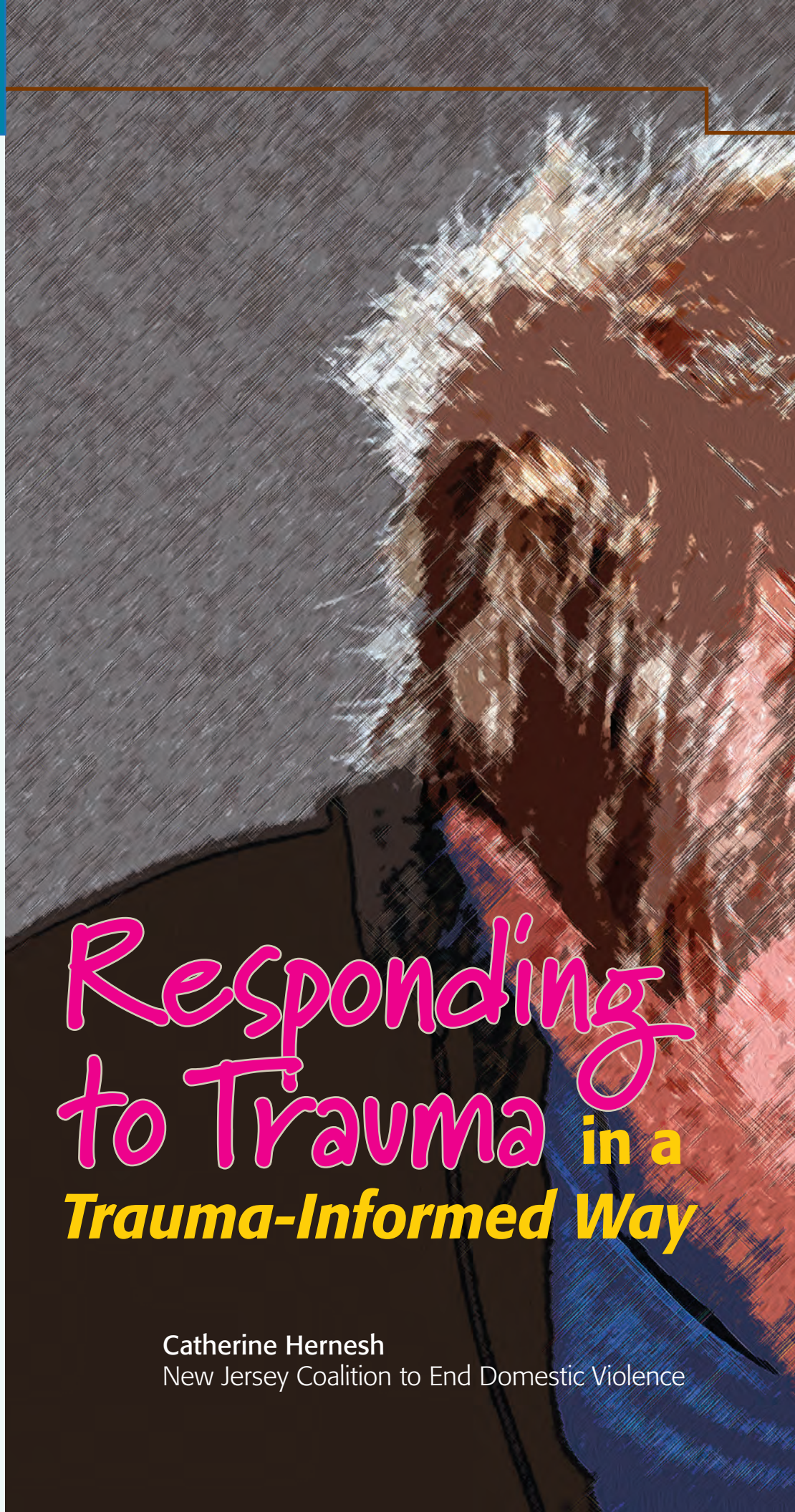
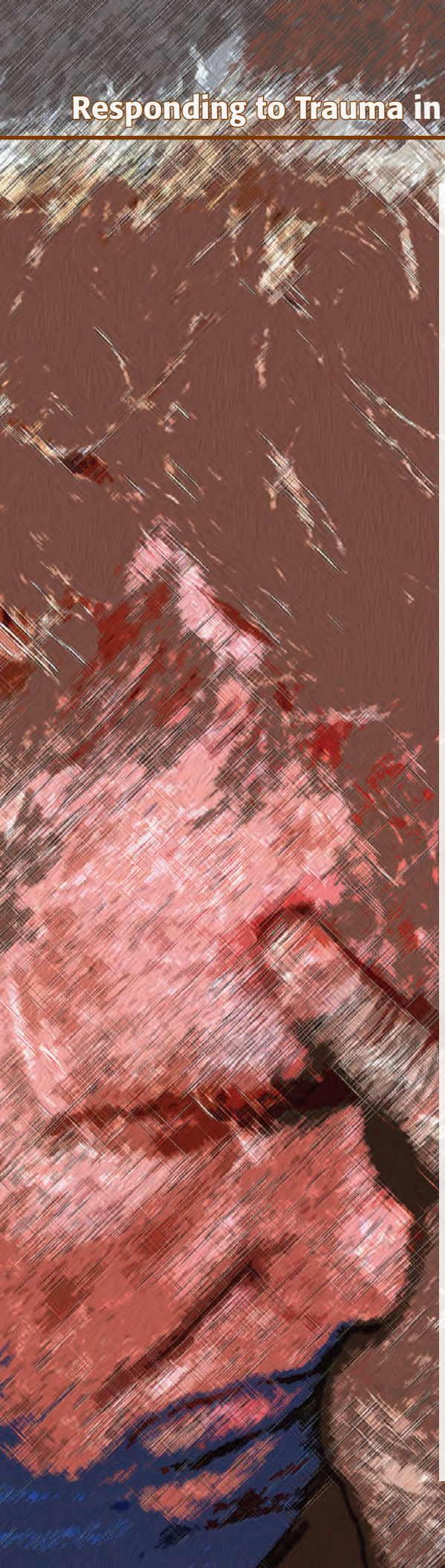


Responding to Trauma in a Trauma-Informed Way

Catherine Hernesh
New Jersey Coalition to End Domestic Violence

Responding to Trauma in a Trauma-Informed Way



As a domestic violence advocate and now, trainer, I have always worked to improve my knowledge about how best to support clients, evolving as new interventions have developed over time. In the past few years, I have seen the term "trauma informed care" move to the forefront for virtually all mental health/healthcare service providers. As I learned about what it means to be trauma informed and provide services from that perspective, I discovered two things: (1) being trauma informed is wholly client centered; and, (2) trauma informed means more than we think. The purpose of this paper is to discuss what it truly means to be trauma informed, so that we can approach all who we serve in this sensitive, enlightened, human way.

In order to be trauma informed, we must know what we mean when we say, "trauma." According to the American Psychological Association, (psychological) trauma is, "an emotional response to a terrible event." Psychologically traumatic events really refer to extreme stressors that overwhelm a person's ability to cope, that cause someone to fear for their physical and emotional safety, even for their very lives. People of all races, ethnicities, religions, cultural backgrounds, genders, gender identities – everyone – is vulnerable to being traumatized, but not necessarily everyone will be traumatized by the same events or in the same way or to the same level.[1]

The above definition of trauma includes responses to powerful incidents like accidents and natural disasters, crimes, surgeries, deaths, and other violent events and events of loss; it also includes intra-familial and intimate relationship violence in all their forms. This definition functions as a starting point for our understanding of how a survivor is experiencing or has experienced the events and conditions of his/her life.[1]

What this really means is, whether or not an event was traumatic is defined by the survivor, not by the event itself, not by the observer or clinician. The same event experienced by two different people could be traumatic for one, not for the other. Ultimately it is any event that causes the person experiencing it to fear for their emotional safety, physical safety, or life.

Okay, so trauma is an extreme, negative event in a person's life. Extreme, so it must be rare, right? Well, the first National Comorbidity Study (1990 – 1992) revealed how rampant traumas actually were in the lives of the general population of the United States. The study of over 8,000 people ages 15-54 showed that nearly 61% of men and over 51% of women reported experiencing at least one trauma in their lifetime, with witnessing a trauma, being involved in a natural disaster, and/or experiencing a life-threatening accident ranking as the most common events.[2] Emotional trauma, it seems, is not unusual. Additionally, the National Intimate Partner and Sexual Violence Survey (2010) collected data from men and women aged 18 and over in the United States about victimization from intimate partner violence, sexual violence, and stalking. Results indicated that over 62% of female victims and over 16% of male victims of rape, physical violence, and/or stalking by an intimate partner reported experiencing at least one symptom of post-traumatic stress disorder (PTSD). Couple that information with the overlap of domestic violence and HIV-positive status

Responding to Trauma in a Trauma-Informed Way

(numerous studies have shown the rate of intimate partner violence among HIV-positive women to be 55%, twice the national average), and it is very likely that the clients you and I encounter will be trauma survivors, and will be exhibiting a trauma response.[3]

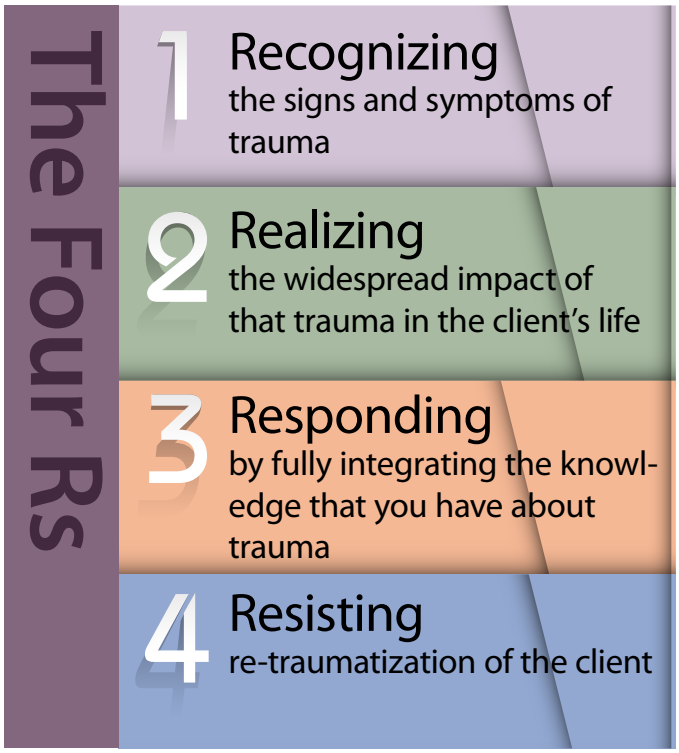
What do I mean by trauma response? In addition to knowing what it means to have survived a trauma, and how common that is, in order to provide trauma informed services we must understand how that impacts the client, and the behaviors that can result. Simply put, in the brain, there are several chemical and biological imbalances that can present after trauma, and we will observe brain function dysregulations. There will be overstimulation of the hypothalamus and the amygdala, and an underactive hippocampus, all created by the release of chemicals such as adrenaline and cortisol into our system, often called the "stress response." When this occurs, the individual can get stuck in a sort of "loop" after the trauma. The loop is this part of the brain perceiving threats in an ongoing way, causing the "fight, flight, or freeze" survival response to be continually active within the traumatized person. From this, we may observe the client who displays hypervigilant and hyper-reactive behaviors. We may also observe what appears to be a lack of focus, inability to recall specific details of the trauma, and we may even observe some challenging behaviors, such as irritability. The trauma survivor may exhibit a diminished ability to regulate their emotional responses. These are all the observable manifestations of a generalized trauma response.

In addition to all of that, there is what is known as "complex trauma," a term used to describe the problem of a child being exposed to multiple or prolonged traumatic events and the impact of this exposure on their development. The National Child Traumatic Stress Network describes it this way:

> "Typically, complex trauma exposure involves the simultaneous or sequential occurrence of child maltreatment—including psychological maltreatment, neglect, physical and sexual abuse, and domestic violence—that is chronic, begins in early childhood, and occurs within the primary caregiving system. Exposure to these initial traumatic experiences—and the resulting emotional dysregulation and the loss of safety, direction, and the ability to detect or respond to danger cues—often sets off a chain of events leading to subsequent or repeated trauma exposure in adolescence and adulthood."[4]

What this means is, children who are abused, violated, neglected, or in any way have the world rendered scary and unsafe by their parents or other primary caregivers, have increased vulnerabilities as they grow, and in their adult lives. That means that they are more likely to suffer additional traumas as adults, such as intimate partner violence and HIV-positive status, and because of their history, their reactions are likely to be more severe than those of the general population in a trauma situation.

This assertion is borne out in studies[5,6] which indicate that elevated levels of stress chemicals in brains during childhood trauma can negatively impact brain development in regard to maturation, as well as areas concerned with social affiliation and support, trust, and attachment. It is also supported by the Adverse Childhood Experiences (ACE) study,



a joint survey of the CDC and Kaiser Permanente which looked at childhood abuse and neglect and their impact on health and well-being later in life. The ACE study revealed that almost 2/3 of respondents had at least one ACE during their developmental years, and more than 1/5 had three or more ACEs. This is significant, because the survey, which continues to receive periodic updates about the medical status/morbidity/mortality of the participants, showed that risk for alcoholism, depression, illicit drug use and abuse, STDs, and myriad life-threatening and chronic illnesses increases as the number of ACEs in one's life increase.[7] This explains, at least in part, why so many of the clients that we see have long histories of multiple abuses throughout their

lives. It also helps us to understand that those trauma-surviving children, who experience additional trauma as adults, will frequently be behaving based on ALL of the trauma they have experienced, with difficulties in trusting and attaching, accepting support and engaging in social relationships, from the "wounded child" who still lives within.

Additionally, people at the highest risk of trauma and those with the most difficulty working through trauma have usually come from a family where there was a trauma in their parents and often in their grandparents lives – we are talking about intergenerational trauma. The director of the Atlanta Mindfulness Institute describes it in this way: "Where trauma has been untreated, what is fairly common is that the untreated trauma in the parent is transmitted to the child through the attachment bond and through the messaging about self and the world, safety, and danger."[8]

So, that is a lot of trauma, and there is more, much more than I can include in this brief article if I am to discuss how to respond to the trauma. You are now, basically, "trauma-informed," although I urge you to do a deeper dive on what I have discussed above, as well as PTSD and complex PTSD. The question now is, how do you use this knowledge to respond to the client in front of you?

To be clear, if you are not a trained therapist, clinician, or mental health counselor, you do not begin counseling the client (although the client will benefit from a referral to a trained, trauma informed clinician). What you will do is, recognize that the person in front of you is having a trauma reaction, and you'll respond to the person, not the reaction. What that really means is, using supportive language and offering appropriate resources that will help the person in front of you build on their strengths.

A key component to any trauma informed agency, organization, or system, is common language. The common language is sometimes called the "Four R's" - recognizing the signs and symptoms of trauma, realizing the widespread impact of that trauma in the client's life, responding by fully integrating the knowledge that you have about trauma, and resisting retraumatization of the client.[9] This is not only the common language but also the foundation for working in a trauma informed way. Working in this way helps to create a safe environment in which the client can begin to heal. When we recognize the signs and symptoms of trauma, we can respond in a supportive way to the client's need, rather than becoming defensive about a client's actions. Responding by fully integrating knowledge can be as simple as helping a client that has been triggered focus on the here and now (grounding and mindfulness techniques are very useful here). Remember, that irritable, "challenging" client in front of you is accustomed to being met with aggression and challenge; the kindness that you can provide is a powerful therapeutic tool.

An additional, crucial aspect of being trauma informed is that supervisors regularly support front line staff around trauma issues and give opportunities to process, so that workers do not feel isolated and develop vicarious trauma, compassion fatigue, and ultimately, burnout. So, trauma informed practices are wonderful because staff will understand what they are seeing and respond supportively and appropriately, therefore NOT retraumatizing the client. Staff in turn is supported in that approach, so that they can come back and do it again the next day.

Finally, trauma experts strongly suggest that agencies have set policy or guidelines for front line staff on engaging and referring clients with trauma symptoms, and that all clients are screened at intake for trauma history and exposure. In this way, trauma survivors will be met through a trauma informed lens at every step in their journey with your organization.❖

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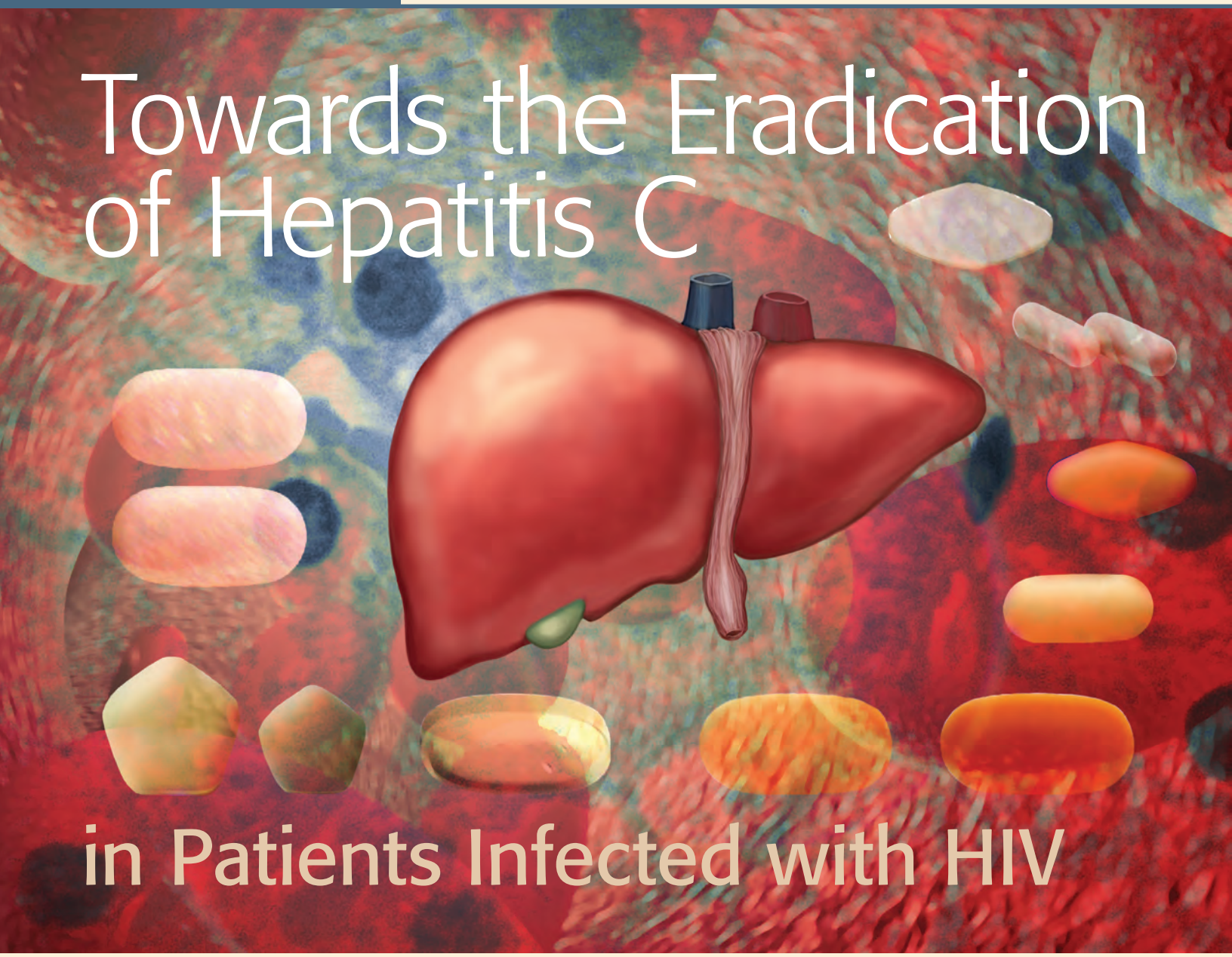
Towards the Eradication of Hepatitis C in Patients Infected with HIV



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INTRODUCTION

Chronic hepatitis C virus (HCV) infection is associated with increased mortality and morbidity in people living with human immunodeficiency virus (HIV) [PLWH]. Therefore, it is of utmost importance to cure any case of HCV in this patient population regardless of the degree of liver fibrosis. In the era of interferon therapy, advances towards a cure for HCV in co-infected patients were slow and largely unsuccessful. This was mainly due to the many contra-indications with treatment, as well as low efficacy and high degrees of toxicity. This has all changed with the advent of the direct-acting antiviral (DDA) agents. In fact, the tolerability and response rates with these new treatment regimens are probably identical between PLWH and HIV-uninfected individuals. The only minor challenge faced in the treatment of HCV in co-infected patients with DAAs is the recognition of potential drug-drug interaction (ddI) with antiretroviral therapy (ART). This article will review and summarize data in co-infection trials, with particular emphasis on ddI between DAAs and ART.

EPIDEMIOLOGY

HIV and HCV share the same mode of transmission, mainly blood and sexual exposure. The infection rates of each virus depend on their prevalence within the community. An estimated 25% of PLWH in the US are co-infected with HCV, and the prevalence of HCV can be up to 90%

among HIV-infected injection drug users.[1] Thus, the US Public Health Service and Infectious Diseases Society of America (IDSA) guidelines recommend that all HIV-infected persons be screened for HCV infection. Screening may be repeated annually in patients that are at particularly high risk of acquiring HCV.[2]

How Does HIV Affect HCV?

The effects of HCV are augmented in PLWH when compared to those not infected with HIV. This is most likely a consequence of their immunodeficiency. Co-infected individuals are less likely to naturally clear acute HCV infection as opposed to mono-infected patients.[3] Acute HCV infection is defined as a positive viral load (VL) with a negative HCV antibody. Furthermore, co-infected patients have a more accelerated rate of liver fibrosis and increased frequency of liver decompensation and death.[4,5,6]

How Does HCV Affect HIV?

HCV also contributes towards worsening HIV effects by furthering immune dysregulation generated by a chronic inflammatory state. This concept was addressed by Zaegel-Faucher et al in a retrospective review of PLWH with undetectable HIV VL for at least 3 years which concluded that both CD4+ percentage and CD4/CD8 ratio were lower in co-infected patients compared to those without HCV infection.[7] It is likely that this immune dysregulation is a major contributor towards the aforementioned increase in mortality and morbidity in co-infected patients, including those that are non-liver related.[8] Co-infected patients also have increased incidence of drug-induced liver injury from concurrent ART use.[9,10] Therefore, the chances of ART-associated drug-induced liver injury may be decreased after successfully curing HCV infection.[9,10]

Pre-Treatment Assessments

The data clearly shows an advantage

Screen all HIV-infected persons for HCV

Screen annually in patients who are high risk of aquiring HCV.

to eradicating HCV in co-infected PLWH.[11] Thus, the first step in treatment is identifying co-infected patients. The US Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents recommend baseline testing for HCV, as well as repeat testing for at-risk patients or when otherwise clinically indicated.[12]

It is well accepted that suppressing HIV disease decreases the rate of liver fibrosis progression in those with HCV.[13] Most of the DAA trials enrolled co-infected patients who were receiving ART with an undetectable HIV VL and a CD4 count >350 cells/mL. The recommended therapy for HCV is the same for patients co-infected with HIV, with the added consideration of potential ddI between ART and DAAs. In order to make a decision about the most appropriate HCV regimen for a particular patient regardless of co-infection, the provider must obtain the following information:

1. HCV VL; ideally two VL measurements at least 6 months apart to establish chronicity of HCV disease.
2. HCV genotype (GT); in certain genotypes it may also be useful to have resistance testing available.
3. Prior treatment history of HCV; document the agents that have been used in the past with knowledge of "on treatment failure" or relapse, as opposed to re-infection.
4. Determine the stage of liver fibrosis based on shear wave elastography measurement and Fibrosis-4 (FIB-4) score; no cirrhosis, compensated cirrhosis, or decompensated cirrhosis.
5. Estimated glomerular filtration rate; to establish which agents are contraindicated due to decreased renal function.
6. Evaluate liver function tests and platelet count.
7. Current medications (including over the counter drugs); in order to avoid potential ddI.

Providers can then choose between specific HCV treatment regimens based on the above parameters. Assuming that the PLWH has an undetectable HIV VL, or a normal CD4+ count if not receiving any ART, as well as a reasonable life expectancy (more than 12 months), patients will have a high prospect of achieving a sustained virologic response at 12 weeks post therapy (SVR12).[14] Figure 1 illustrates the factors involved in the pre-assessment process for choosing the best DAA for the treatment of HCV in co-infected patients.

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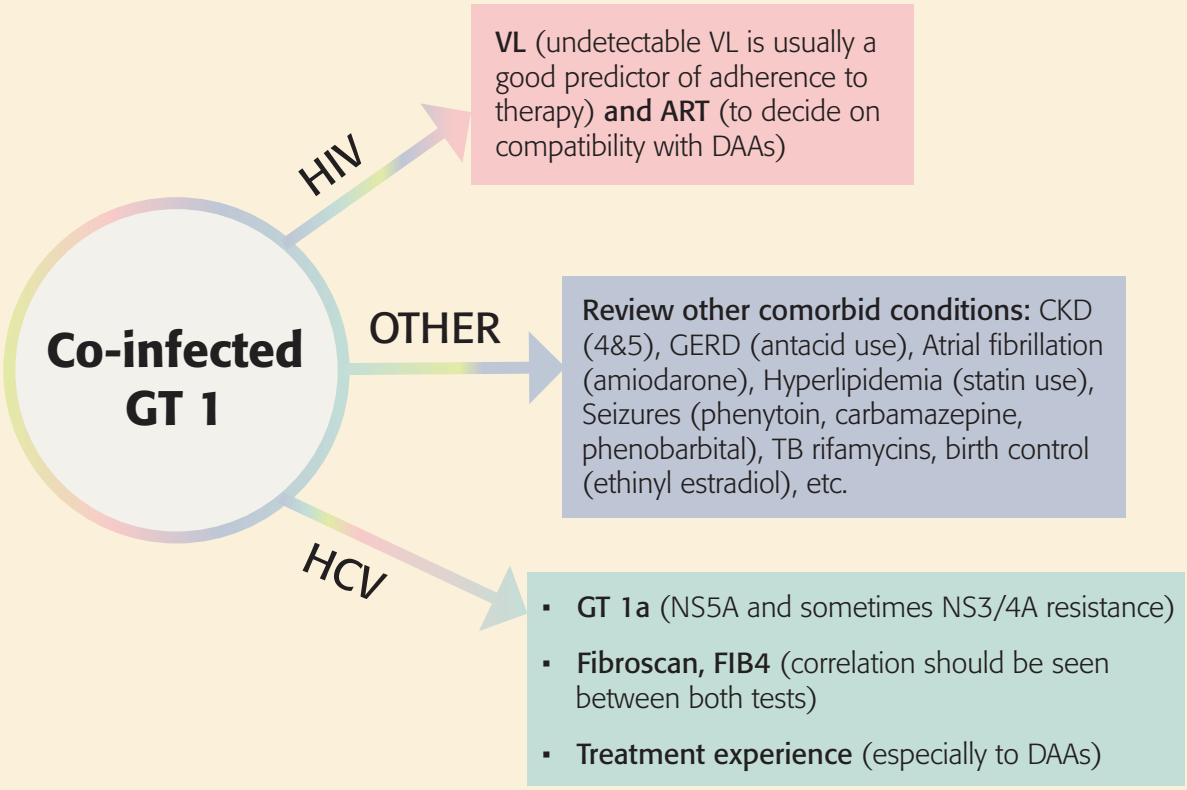

DAA TREATMENT OPTIONS

Grazoprevir 100 mg/ Elbatasvir 50 mg

Grazoprevir 100 mg/elbatasvir 50 mg (Zepatier™) is a one-tablet fixed-dose combination (FDC) containing elbatasvir, an NS5A inhibitor, and grazoprevir, an NS3/4A protease inhibitor (PI). It is indicated with or without ribavirin (RBV) for genotype (GT) 1 or 4 infection in adults (≥ 18 years). It does not require dose adjustment in patients with chronic kidney disease (CKD) stage 4 or 5, and is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh Turcotte [CPT] classification B or C).[15]

Rockstroh et al conducted an open-label, multi-center, phase 3, single-arm study of co-infected participants with GT 1, 4, and 6. All participants received grazoprevir 100 mg/elbatasvir 50 mg one tablet daily for 12 weeks. SVR12 was achieved by 210/218 participants (96%) enrolled in the study (95% Confidence Interval (CI): 92·9-98·4). One participant did not achieve SVR12 because of a non-virological reason and seven participants without cirrhosis relapsed (two subsequently confirmed as re-infections). The most common adverse events were fatigue (13%), headache (12%), and nausea (9%). No participants discontinued treatment because of an adverse event. Two participants receiving ART had transient HIV viremia.[16]

The FDA approved dosing for grazoprevir 100 mg/elbatasvir 50 mg in GT 1a HCV-infected, treatment-naïve patients. It is also approved in combination with weight-based RBV for 16 weeks in pegylated interferon/RBV-experienced patients with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93. Grazoprevir/elbatasvir/RBV for 16 weeks is also approved for treatment-experienced patients with GT 4. Duration of therapy is 12 weeks for all other GT 1 and GT 4 patients. RBV must also be added to GT 1b and GT 1a patients with no NS5A polymorphism if they have previously failed a protease inhibitor (PI)-based ART regimen (ie, boceprevir, telaprevir, and simeprevir).

Because grazoprevir is a substrate of OATP1B1/3 transporters, any inhibitor of this enzyme system is contraindicated (ie, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, and cyclosporine). Elbasvir and grazoprevir are both substrates of CYP3A and P-glycoprotein (P-gp). Thus, co-administration with strong CYP3A inducers is also contraindicated (ie, phenytoin, carbamazepine, efavirenz, rifampin, and St. John's wart).

Grazoprevir/elbatasvir should only be used with an ART regimen without clinically significant interactions. These regimens include abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.

Paritaprevir 75 mg/Ritonavir 50 mg/Ombitasvir 12.5 mg ± Dasabuvir 250 mg

Two tablets of the FDC containing paritaprevir (PI), ritonavir (the "booster" for the PI), and ombitasvir (an NS5A inhibitor) given daily, combined with dasabuvir (a non-nucleoside NS5B inhibitor) given as one tablet twice a day is available as Viekira pak™

or as Viekira Pak XR™ given as three tablets once a day. It is indicated for 12 weeks duration for patients with GT 1a, and in combination with RBV for 12 weeks for non-cirrhotic GT 1a patients.[17] Technivie™ consists of paritaprevir/ritonavir/ombitasvir without dasabuvir and is indicated in combination with RBV for 12 weeks for GT 4 non-cirrhotic patients.[18]

Sulkowski et al conducted a pilot study of paritaprevir/ritonavir/ombitasvir + dasabuvir with RBV for 12 or 24 weeks in 63 participants co-infected with GT 1. All participants had suppressed plasma HIV-1 RNA while taking a stable atazanavir- or raltegravir-based ART regimen. SVR12 was achieved by 29 of 31 in the 12 weeks arm (94%; 95% CI, 79%-98%) and 29 of 32 participants (91%; 95% CI, 76%-97%) in the 24 weeks arm. Of the five participants who did not achieve SVR12, one withdrew consent, two had confirmed virologic relapse or breakthrough, and two were re-infected. The most common treatment-emergent adverse events were fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). No serious adverse events were reported and none led to discontinuation of therapy. Also, no participant had a confirmed HIV-1 breakthrough of ≥200 copies/mL during treatment.[19]

Paritaprevir/ritonavir/ombitasvir + dasabuvir is contraindicated in patients with severe hepatic impairment, detectable HIV VL, and those receiving drugs that are contraindicated with ritonavir. Also, because of the potential to increase dasabuvir plasma concentrations as well as increase the risk for QT prolongation, drugs that are strong inhibitors of CYP2C8 (eg, gemfibrozil) are also contraindicated with paritaprevir/ritonavir/ombitasvir + dasabuvir. Lastly, products containing ethinyl estradiol should be avoided with paritaprevir/ritonavir/ombitasvir + dasabuvir due to the potential for hepatotoxicity.

ART that are safe to use with paritaprevir/ritonavir/ombitasvir + dasabuvir include atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir. The dose of ritonavir used for boosting atazanavir may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir + dasabuvir and then restarted when HCV treatment is completed. Atazanavir should also be administered at the same time as the FDC tablets.

Sofosbuvir 400 mg + Daclatasvir 60 mg

Daclatasvir is an NS5A inhibitor and sofosbuvir is a nucleotide analog inhibitor of NS5B (polymerase inhibitor). Sofosbuvir + daclatasvir with or without RBV for 12 weeks is indicated for the treatment of GT 1 and 3. Baseline NS5A resistance testing should be considered in patients with cirrhosis. It is suggested that RBV be added in the presence of polymorphism, especially at amino acid 93.

ALLY-2 is a randomized, open-label study in co-infected PLWH who received eight or 12 weeks of once daily daclatasvir 60 mg (dose adjusted as necessary for concomitant ART) + sofosbuvir 400 mg. Results were stratified by ART class for the 151 participants who received 12 weeks of sofosbuvir + daclatasvir. Fifty-one participants were treatment-experienced, 100 were treatment-naive, 89% were male, and 33% black. Furthermore, 69% were GT 1a, 15% were GT 1b, 8% were GT 2, 6% were GT 3, and 2% were GT 4. Ninety-seven percent of patients achieved SVR12. No discontinuations were attributed to treatment-related adverse events.[20]

The only contraindication for this regimen is concomitant use of strong inducers of CYP3A, which includes phenytoin, carbamazepine, rifampin, and St. John's wart.[21] Another limitation is the fact that there is no dosage recommendation for sofosbuvir in patients with CKD 4 and 5.[22] This combination can be used with almost all ART regimens. However, daclatasvir must be decreased to 30 mg daily when combined with ritonavir-boosted atazanavir, and must be increased to 90 mg daily when given with efavirenz or etravirine.

Sofosbuvir 400 mg/ Ledipasvir 90 mg

Sofosbuvir 400 mg/ledipasvir 90 mg (Harvoni™) is a FDC containing ledipasvir, an NS5A inhibitor, and sofosbuvir. It is indicated for the treatment of GT 1, 4, 5, and 6. Duration of therapy is generally 12 weeks. The only indication for 24 weeks of treatment

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with sofosbuvir 400 mg/ledipasvir 90 mg is for treatment-experienced, GT 1, compensated cirrhosis (CPT A). RBV is added for GT 1 patients with decompensated cirrhosis (CPT B or C), as well as post-liver transplant patients with GT 1 or 4.[23] Although sofosbuvir 400 mg/ledipasvir 90 mg can be used for only eight weeks in GT 1, treatment-naive, non-cirrhotic patients with HCV VL <6,000,000 IU/mL, the AASLD/IDSA guidelines advise against this shorter duration of therapy in co-infected patients.[24]

The ION-4 Phase 3 trial evaluated the efficacy and safety of sofosbuvir 400 mg/ledipasvir 90 mg in co-infected PLWH receiving ART. The study included treatment-naive and treatment-experienced participants on stable, approved ART who received sofosbuvir 400 mg/ledipasvir 90 mg once daily for 12 weeks. Permitted concomitant ART included tenofovir disoproxil fumarate (TDF) with emtricitabine and raltegravir (44%), efavirenz (48%), and rilpivirine (9%). Of the 335 enrolled participants, 75% were GT 1a, 23% were GT 1b, and 2% were GT 4. Eighty-two percent of participants were male, 61% were white, and 38% were black. The mean age was 52 years (range 26 to 72). The mean baseline HCV VL was 6.7 log10 IU/mL (range 4.1–7.8) and the median baseline CD4 count was 628 cells/mL. Twenty percent of participants had compensated cirrhosis and 55% were treatment-experienced. Ninety-six percent of participants achieved SVR12. Two participants had on-treatment virologic failure. Furthermore, 10 participants had virologic relapse after the discontinuation of treatment. All 10 of these participants were black and eight were also taking efavirenz. One participant died secondary to endocarditis at week four of therapy. In multivariate analysis, only black ethnicity was associated with a lower rate of SVR. No participants had confirmed HIV virologic rebound. Adverse events occurred in ≥10% of participants and included headache (25%), fatigue (21%), and diarrhea (11%). No participants discontinued the study drug due to an adverse event.[25]

There are certain ddIs that should be considered before starting therapy with sofosbuvir/ledipasvir. Ledipasvir solubility decreases as gastric pH increases. Thus, drugs that increase gastric pH are expected to decrease concentration of ledipasvir. If antacid therapy is required, sofosbuvir/ledipasvir should be given at times when the gastric pH is expected to be at its lowest. Omeprazole may be given with sofosbuvir 400 mg/ledipasvir 90 mg as long as the dosage does not exceed 20 mg daily. Also, sofosbuvir/ledipasvir should not be combined with rosuvastatin. Sofosbuvir/ledipasvir may significantly increase the concentration of rosuvastatin, resulting in rhabdomyolisis. Furthermore, ledipasvir increases tenofovir (in TDF form) levels, and, therefore sofosbuvir/ledipasvir is not recommended in combination with elvitegravir/cobicistat/emtricitabine/TDF. Sofosbuvir/ledipasvir use in patients on TDF and a boosted protease inhibitor should be used with caution and requires close monitoring of renal function. In these situations it is probably safer to switch TDF to tenofovir alafenamide (TAF) in order to decrease the chance of nephrotoxicity. Sofosbuvir use should also be restricted in patients with CKD stage 4 and 5.[26]

Sofosbuvir 400 mg + Simeprevir 150 mg

Simeprevir, an NS3/4A protease inhibitor, in combination with sofosbuvir is indicated for GT 1 patients who have not failed prior therapy with a PI.[27] Duration of therapy is 12 weeks for non-cirrhotic patients and 24 weeks for cirrhotic patients. In patients with decompensated cirrhosis and GT 1a infection, consider testing for the presence NS3/4A Q80K polymorphism. Data on the use of sofosbuvir + simeprevir in co-infected patients comes from real-life experience. A report from Northwestern University Viral Hepatitis Registry by Hawkins et al showed that out of 33 co-infected patients treated with sofosbuvir + simeprevir, only one relapsed. Also, none of these patients had to stop therapy due to side effects.[28]

Simeprevir is primarily metabolized by CYP3A4. It is also an inhibitor of CYP1A2, OATP1B1/3, P-gp, and BCRP transporters. Simeprevir is safe to use in combination with abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir (and probably dolutegravir), rilpivirine, and tenofovir. Sofosbuvir + simeprevir should be used with caution when in combination with amiodarone due to a potential ddI with sofosbuvir that may result in serious symptomatic bradycardia. Furthermore, simeprevir may cause hepatic decompensation in patients with advanced liver fibrosis. Finally, simeprevir can cause photosensitivity and patients should be advised to use sunscreen and limit sun exposure during sofosbuvir + simeprevir therapy.

Sofosbuvir 400 mg/ Velpatasvir 100 mg

Sofosbuvir 400 mg/velpatasvir 100 mg (Epclusa™) is the newest drug approved in the US for the treatment of HCV; a FDC that combines sofosbuvir with velpatasvir, an NS5A inhibitor. This regimen is indicated for GT 1, 2, 3, 4, 5, and 6 in patients with or without compensated cirrhosis, and consists of one tablet once a day for 12 weeks. RBV is added for patients with decompensated cirrhosis (CPT B and C).[29]

Because it contains sofosbuvir, no dose recommendation can be given for patients with eGFR<30 ml/min. Also, like ledipasvir, velpatasvir solubility decreases as pH increases. Therefore, drugs that increase gastric pH are expected to decrease concentration of velpatasvir. The list of ddI for sofosbuvir/velpatasvir is very similar to that of sofosbuvir/ledipasvir. Sofosbuvir/velpatasvir can be used with most ART, except efavirenz, etravirine, tipranavir, and probably nevirapine. Also, velpatasvir in combination with TDF increases tenofovir levels, especially with concomitant use of cobicistat or ritonavir. Therefore, it would be prudent to switch patients with renal insufficiency to TAF before starting sofosbuvir/velpatasvir.

The ASTRAL 5 study presented at the European Association for the Study of the Liver (EASL) meeting in April 2016 was a single-arm, open-label, multicenter phase 3 trial of sofosbuvir 400 mg/velpatasvir 100 mg in HIV/HCV co-infected participants. The study enrolled a total of 106 participants, 91 male and 48 black, with a mean age of 54 (range 25 to 72). Sixty-six participants had GT 1a, 12 had GT 1b, 11 had GT 2, 12 had GT 3, and five had GT 4. Nineteen participants had compensated cirrhosis and 31 participants were treatment-experienced, but none were previously treated with NS5A or NS5B inhibitors. Participants were all on a stable ART for at least eight weeks, with HIV VL <50 copies/mL and CD4+ >100 cells/mL. ART regimens consisted of atazanavir, darunavir, or lopinavir/ritonavir (47%); the integrase inhibitors raltegravir or elvitegravir (34%); and the NNRTI rilpivirine (12%). NRTI backbones included TDF/emtricitabine (86%), tenofovir in an unboosted regimen (33%), and abacavir/lamivudine (14%). All participants received one tablet of sofosbuvir 400 mg/velpatasvir 100 mg once-daily for 12 weeks. The overall SVR12 rate was 95% (99/104), with two participants still undergoing post-treatment follow-up. Non-responders included two who relapsed, one lost to follow-up, and one withdrawal of consent. Sofosbuvir 400 mg/velpatasvir 100 mg was generally safe and well tolerated, with only two serious adverse events and two treatment discontinuations due to adverse events (one of whom achieved SVR12). The most frequently reported side effects were fatigue (25%) and headache (13%). The most common laboratory abnormality was elevated bilirubin in participants taking boosted atazanavir. Of particular note, 56 participants with CrCl > 60 mL/min on ART consisting of TDF with ritonavir-boosted or cobicistat-boosted regimens did not develop renal toxicity. Lastly, no one experienced HIV viral rebound while on treatment.[30]

Table 1. Specific DAA Indications (based on HCV genotype and polymorphism)

	NS3/4A	NS5A	NN NS5B	N NS5B	GT1	GT2	GT3	GT4	GT5	GT6
G/E	X	X			X			X		
r/P/O/D	X	X	X		X					
r/P/O	X	X						X		
S/Dak		X		X	X		X			
S/L		X		X	X			X	X	X
S/Si	X			X	X					
S/V		X		X	X	X	X	X	X	X

G/E: grazoprevir/elbatasvir; r/P/O/D: ritonavir/paritaprevir/ombitasvir/dasabuvir; r/P/O: ritonavir/paritaprevir/ombitasvir; S/Dak; sofosbuvir/daclatasvir; S/L: sofosbuvir/ledipasvir; S/Si: sofosbuvir/simeprevir; S/V: sofosbuvir/velpatasvir; NS3/4A: protease inhibitor; NN NS5B: non-nucleoside polymerase inhibitor; N NS5B: nucleoside polymerase inhibitor; GT: genotype

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Drug Interactions with DAA and ART

As previously stated, in order to better preserve the immune system, decrease the state of persistent inflammation, and reduce the degree of liver fibrosis, it is absolutely essential to treat all cases of HCV in co-infected patients. With the multitude of DAA regimen options available, medical providers rarely have to switch ART prior to HCV treatment. However, there are certain contraindications to combined DAA and ART therapies due to ddIs.

One such contraindication is combining sofosbuvir with tipranavir.[31] Because tipranavir is a potent P-gp inducer, it decreases sofosbuvir levels.[31] Furthermore, tipranavir is often used with ritonavir, a potent CYP 450 3A inhibitor, and this ART regimen should be avoided in combination with grazoprevir and paritepravir due to its potential to increase the levels of these DAAs.[31] Nevirapine should also not be taken with DAAs because of its effects on inducing CYP 450 3A and 2B6 enzymes, and studies concerning this combination are lacking.[31] Instead, it is suggested that nevirapine be switched to a rilpivirine-based ART therapy since it has been well studied in multiple switch trials and was found only to have minimal ddI with DAAs.[32] Table 2 summarizes the choice of DAAs for HCV with co-infection based on the ART regimen.

Here are some practical examples:

In a patient with GT 2 infection, all efforts should be made to treat them with sofosbuvir 400 mg/velpatasvir 100 mg for 12 weeks.[33] If the patient is an efavirenz-based ART therapy it should be switched to rilpivirine. Furthermore, proton pump inhibitors should be discontinued for the 12 weeks duration of therapy.

Those with advanced chronic kidney disease (stage 4 and 5) should be treated with grazoprevir 100 mg/elbatasvir 50 mg.[34] Patients not resistant to integrase inhibitors should be switched to a dolutegravir or raltegravir-based ART regimen.

Those with advanced liver fibrosis (CPT B or C) would benefit most from a DAA regimen consisting of sofosbuvir and either ledipasvir, daclatasvir, or velpatasvir.

Patients receiving elvitegravir/cobicistat/emtricitabine/TDF or TDF with a boosted protease inhibitor as their stable ART should be switched to elvitegravir/cobicistat/ emtricitabine/TAF and TAF respectively if they require sofosbuvir/ledipasvir for the treatment of their HCV.

Finally, when taking DAAs, all concomitant medications should be reduced to only those that are absolutely necessary. Drugs that should be discontinued include antacids, statins, vitamins, NSAIDs, and any over the counter supplements.

On-Treatment Assessments

Routine testing during treatment including complete blood count and complete metabolic panel should be trended from baseline in order to identify potential AEs from DAAs. Furthermore, specific on-treatment assessments are recommended for the use of grazoprevir/elbatasvir, paritaprevir /ritonavir/ombitasvir + dasabuvir, and RBV. Clinical trials found that both grazoprevir/elbatasvir and paritaprevir/ritonavir/ombitasvir + dasabuvir increased alanine aminotransferase (ALT) to greater than five times the upper limit of normal (ULN) in 1% of patients. Therefore, liver function tests should be repeated at week eight for those on grazoprevir/elbatasvir and at week four for patients on paritaprevir/ritonavir/ombitasvir + dasabuvir, as well as additional repeat testing if clinically warranted. Grazoprevir/elbatasvir and paritaprevir/ritonavir/ombitasvir + dasabuvir should both be discontinued if ALT consistently remains greater than 10 times the ULN or, in the setting of ALT elevation, if patients also develop symptoms or rise in alkaline phosphatase, INR, or conjugated bilirubin. If either of these regimens is combined with RBV, hemoglobin and hematocrit should be checked at week two and week four of treatment due to the risk for hemolytic anemia. Furthermore, RBV has been associated with severe teratogenic effects and, thus, all female patients of childbearing age should have a pregnancy test before the start of treatment and counseled to not get pregnant during therapy.[15,18,35]

Post-Treatment Assessments

HCV VL must be re-checked no earlier than 12 weeks after the end of treatment. If VL remains undetectable, SVR12 has been achieved and the patient is considered cured. Repeat liver enzyme tests, shear wave elastography measurement, and Fibrosis-4 (FIB-4) score should be done to assess any improvement in liver function and in degree of fibrosis. Patients with cirrhosis or advanced fibrosis should be referred to a hepatologist.

Summary

Overall, DAAs are extremely efficacious in the treatment of HCV infection and are associated with minimal AEs as compared to prior therapies. Therefore, all patients with HCV should be treated. This is especially true for those co-infected with HIV since each virus augments the harmful effects of the other. In order to safely treat this patient population, medical professionals must be aware of potential ddI that exists between ART and DAAs. With the many choices of both DAA and ART regimens, many toxicities can be avoided. Understanding these ddIs, along with proper laboratory screening and on-treatment monitoring will allow virtually every co-infected patient to safely and successfully be cured of their HCV. ❖

This article was reviewed for accuracy by Shobha Swaminathan, MD

Towards the Eradication of Hepatitis C in Patients Infected with HIV

New Jersey HIVLinks Winter 2016
HIV, STD, and TB news and information for health professionals

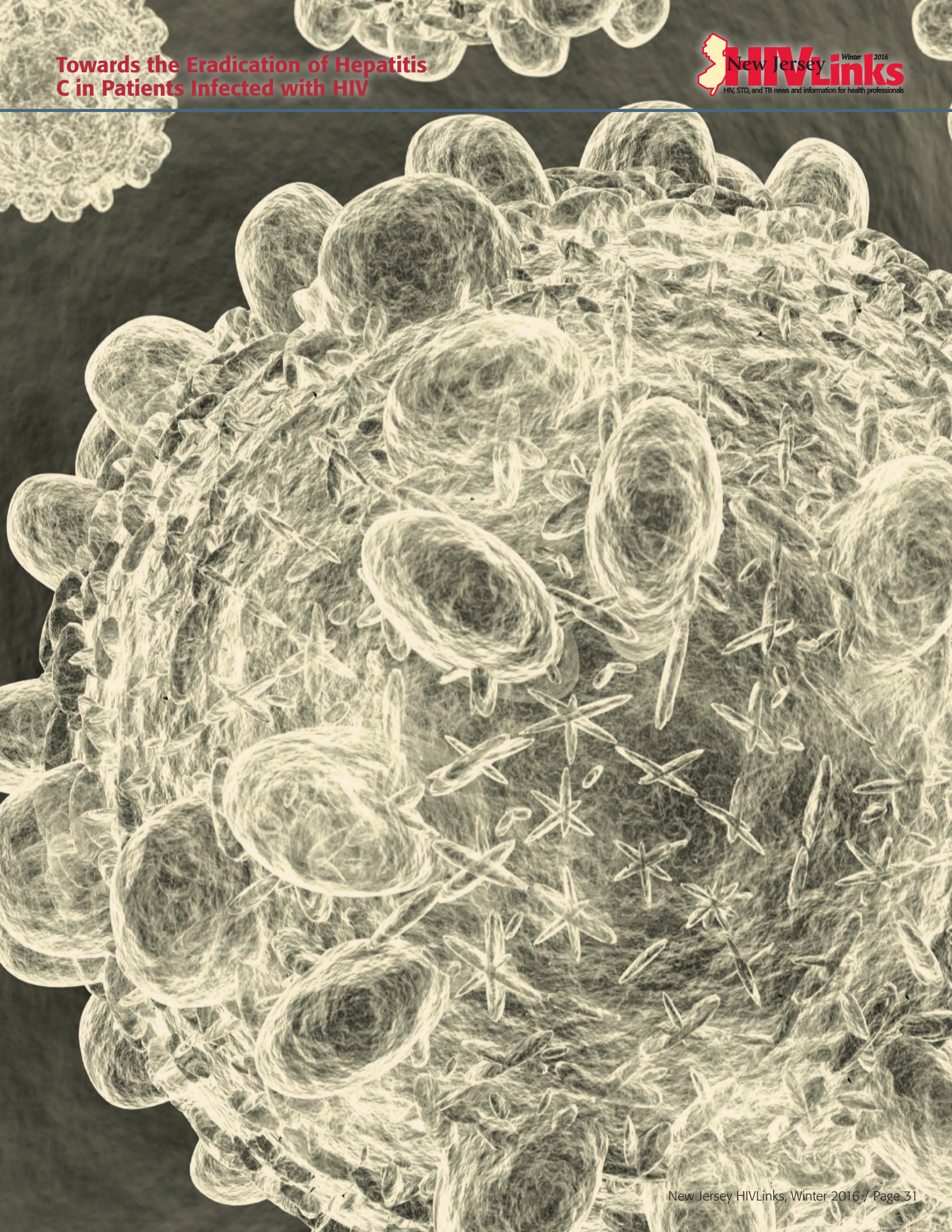

Table 2.

Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults[36]

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/Paritaprevir/ Ritonavir plus Dasabuvir[b]	Simeprevir
Nucleoside Reverse Transcriptase Inhibitors						
3TC	√	√	√	√	√	√
ABC	√	√	√	√	√	√
FTC	√	√	√	√	√	√
TDF	√	√	√ Monitor for TDF toxicity.	√	√	√
TAF	√	√	√	√	√	√
HIV Protease Inhibitors						
ATV (unboosted)	√	√	√	X	√ Reduce ATV dose to 300 mg and take in the morning at same time as ombitasvir/ paritaprevir/ritonavir plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.	X
ATV/r or ATV/c	√ ↓ DCV dose to 30 mg/day	√	√ If PI/r (or ATV/c, DRV/c) is used with TDF, ↑TDF concentrations are expected. If coadministration necessary, monitor for TDF-associated toxicities (see footnotec).	X	√ Take ATV 300 mg in the morning at same time as ombitasvir/paritaprevir/r plus dasubuvir; discontinue RTV or COBI in HIV regimen until HCV therapy completed.	X
DRV/r or DRV/c	√	√		X	X	X
FPV or FPV/r	√	√		X	X	X
LPV/r	√	√		X	X	X
SQV/r	√ ↓ DCV dose to 30 mg/day			X	X	X
TPV/r	?	X	X	X	X	X

table continued on next page

Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults[36]

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/Paritaprevir/ Ritonavir plus Dasabuvir[b]	Simeprevir
Non-Nucleoside Reverse Transcriptase Inhibitors						
EFV	√ ↓ DCV dose to 90 mg/ day	√	√ If used with TDF, monitor for TDF toxicity.	X	X	X
ETR	√ ↓ DCV dose to 90 mg/ day	√		X	X	X
NVP	√ ↓ DCV dose to 90 mg/ day	√		X	X	X
RPV	√	√		√	X	√
Integrase Strand Transfer Inhibitors						
DTG	√	√	√ If used with TDF, monitor for TDF toxicity.	√	√	√
EVG/c/TDF/ FTC	√ ↓ DCV dose to 30 mg/day	√	X	X	X	X
EVG/c/TAF/ FTC	√ ↓ DCV dose to 30 mg/day	√	√	X	X	X
EVG (plus PI/r without COBI)	√ ↓ DCV dose to 30 mg/day for all PI/r, except TPV/r - do not coadminister	Refer to Recommendations for individual ritonavir-boosted PI.				
RAL	√	√	√	√	√	√
CCR5 Antagonist						
MVC	√	√	√	?	X	√

a. Since boceprevir is no longer recommended for HCV treatment and telaprevir is no longer available in the United States, these products have been removed from this table.
b. Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir.
c. Consider alternative HCV or ARV therapy to avoid increases in TDF exposure. If coadministration is necessary, monitor for TDF-associated adverse reactions.

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Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults[36]

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/Paritaprevir/ Ritonavir plus Dasabuvir[b]	Simeprevir

Key to Symbols:
√ = ARV agents that can be used concomitantly
X = ARV agents not recommended
? = data limited or not available on PK interactions with ARV drug

Key to Acronyms:

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; c or COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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