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Planner/Reviewer Financial Disclosures
Planner/Reviewer 1 has been a consultant to Antiva Biosciences, Gilead Sciences, Inc, and ViroPharma, Inc.
Planner/Reviewer 2 has no relevant financial affiliations to disclose.
Planner/Reviewer 3 has no relevant financial affiliations to disclose.

Financial disclosures for members of the IAS–USA Board of Directors and the Editorial Board of Topics in Antiviral Medicine are available online at www.iasusa.org.

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Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in your email address, please create or update your user profile at www.iasusa.org.

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Website: www.iasusa.org

On the Web
Current and previous issues of Topics in Antiviral Medicine (as well as Topics in HIV Medicine) are available online at www.iasusa.org/activities/topics-in-antiviral-medicine.
ISSN 2161-5853 (Online)

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Grant Support
IAS–USA funding comes from a variety of sources. The largest single source of revenue is conference and participant registration fees. This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers.

The 2019 Update of the Drug Resistance Mutations in HIV-1 is a special project funded by the IAS–USA reserve fund.
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Learning Objectives

On completion of this activity, the learner will be able to:

- Describe the impact of the implementation of the Patient Protection and Affordable Care Act (ACA) on the role of the Ryan White/AIDS (RWHAP) in HIV care
- Explain the impact of liver disease as a cause of mortality among individuals with HIV infection
- Describe principles of initiating antiretroviral therapy in treatment-naive patients and the principles of changing therapy based for initial treatment failure

Intended Audience

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and other viral infections and those who are new to HIV care or who want a refresher on the basics of antiretroviral therapy. This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Financial affiliations with commercial entities: Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc and ViViHealthcare. Drs Ginossar, Oetzel, Van Meter, and Gans have no relevant financial affiliations to disclose. Dr Gallant had served as a member of the data safety monitoring board for or as a consultant or an advisor to Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, Theratechnologies, and ViViHealthcare/Glaxo-SmithKline. He had received research grant support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Inc, Merck & Co, Inc, Sangamo BioSciences, and ViViHealthcare/GlaxoSmithKline. He is currently an employee of Gilead Sciences, Inc. Dr Sherman has received grant support or contracts awarded to his institution from AbbVie, Gilead Sciences, Inc, Intercept Pharmaceuticals, Inc, MedImmune, and Merck & Co, Inc; served as an advisor or consultant to UniQure and Inovio Pharmaceuticals; and served on data and safety monitoring boards for Watermark and Medpace. Dr Peters has served as an advisor to Abbott. Her spouse is employed by Hoffman-La Roche. Dr Thomas has no relevant financial affiliations to disclose. Dr Wensing has served on advisory boards for ViViHealthcare, Merck & Co, Inc, Janssen Therapeutics, and Gilead Sciences, Inc, and has received research support from ViViHealthcare, Bristol-Myers Squibb, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc. Dr Charpentier serves as an advisor for ViViHealthcare, Gilead Sciences, Inc, Janssen Therapeutics, and Merck Sharp & Dohme, Inc, and has received research grants from ViViHealthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc. Dr Paredes has received research grants from and has served as an advisor to ViiV Healthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc. Dr Shafer has received research grants from Janssen Therapeutics, Vela Diagnostics, and InSilixa, Inc, and consulting fees from Abbott Diagnostics. Dr Richman has been a consultant to Antiva Biosciences, Gilead Sciences, Inc, and Viroime, Inc.

Independent educational grants for the 2019 Improving the Management of HIV Disease® CME program:

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Review

The Ryan White HIV/AIDS Program After the Patient Protection and Affordable Care Act Full Implementation: A Critical Review of Predictions, Evidence, and Future Directions

Tamar Ginossar, PhD; John Oetzel, PhD; Lindsay Van Meter, JD, MPH; Andrew A. Gans, MPH; Joel E. Gallant, MD, MPH

The Ryan White HIV/AIDS Program (RWHAP) has been effective in serving people living with HIV (PLWH). Our goal was to examine the impact of the implementation of the Affordable Care Act (ACA) on the program’s role in HIV care and its clients. We utilized critical review to synthesize the literature on the anticipated effects of the ACA, and assess the evidence regarding the early effects of the ACA on the program and PLWH who receive RWHAP services. To date, research on the impact of ACA on RWHAP has been fragmented. Despite the expected benefits of the ACA to PLWH, access and linkage to care, reducing inequity in HIV risk and access to care, and coping with comorbidities remain pressing challenges. There are additional gaps following ACA implementation related to immigrant care. RWHAP’s proven success in addressing these challenges, and the political threats to ACA, highlight the need for maintaining the program to meet HIV care needs. More evidence on the role and impact of RWHAP in this new era is needed to guide policy and practice of care for PLWH. Additional research is needed to explore RWHAP care and its clients’ health outcomes following ACA implementation, with a focus on at-risk groups such as immigrants, transgender women, homeless individuals, and PLWH struggling with mental health problems.

Keywords: HIV, Ryan White, Affordable Care Act, ACA, health care

Introduction

In 2014, more than half of the people living with HIV (PLWH) in the United States received services provided by the Ryan White HIV/AIDS Program (RWHAP). This safety-net program provides medication, health care, and wrap-around services for uninsured and underinsured PLWH, with demonstrated effectiveness in increasing continuity of care, engagement in care, and the use of antiretroviral therapy (ART) by its clients. Linkage to care and use of ART are necessary for achieving viral suppression, which in turn leads to improved individual health outcomes and a substantial reduction in HIV transmission. The program was designed to provide a comprehensive array of medical and support services, yet as a payer of the last resort, it cannot fully address the non-HIV-related medical needs of PLWH. Consequently, the implementation of the Affordable Care Act (ACA) raised uncertainty regarding the future need for the program and the care provided to its clients. Whereas numerous reviews and editorials analyzed the anticipated impact of the ACA on HIV care prior to full ACA implementation in 2014, including in the context of RWHAP, we were able to identify only 1 review of the literature on the impact of the ACA after implementation. Although that review included some RWHAP-related data and outlined directions for future research, to our knowledge scholars did not focus on the post-ACA role of the program, the impact of ACA on RWHAP services, or health outcomes of its clients. Such an examination is crucial in view of the pivotal role of the program in HIV care provision, and its implications for policy and practice.

To begin addressing this knowledge gap, we examine the research on the role of the RWHAP before the adoption of the ACA, integrate the literature on the anticipated effects of the ACA on PLWH served by the RWHAP, and examine the evidence on the early effects of the ACA on PLWH served by the RWHAP. To better understand the importance of both the RWHAP and the ACA in care for PLWH, it is important to understand the challenges facing this care.

Challenges in HIV Care in the United States

The availability of ART transformed HIV infection from a terminal illness to a chronic, treatable condition. However, 3 overarching and interrelated challenges loom over HIV care in the United States: inadequate linkage to care, inequity in HIV risk and access
to care, and the high prevalence of comorbidities. Early and continued use of ART results in virologic suppression, which reduces mortality and morbidity, prevents further transmission, and is highly cost-effective. However, many PLWH experience delays in linkage to care, fail to be retained in care, or are unable to adhere to treatment. Consequently, only about half of persons diagnosed with HIV and 30% of PLWH achieve viral suppression in 2016. PLWH who are unaware of their HIV status or who have not achieved viral suppression are at risk of infecting others. With about 38,500 people newly diagnosed with HIV in the United States annually, effective HIV treatment is important not only for the health of individual patients, but also as a crucial public health measure.

A related issue involves disparities in care and health outcomes. At each point of the HIV care continuum, the burden of HIV morbidity and mortality disproportionately affects vulnerable ethnic and racial minorities, young adults, sexual minorities, and people with low-income. The third challenge relates to treatment of comorbidities, including serious mental health disorders, substance use disorders, and chronic hepatitis B or C. Moreover, the prevalence of age-associated comorbidities such as cardiovascular, chronic kidney, and bone diseases is growing, as a result of the aging of the PLWH population, as well as a combination of HIV- and ART-related factors.

These challenges to HIV care are further complicated by barriers created by the complex US health policies and systems, including insufficient medical insurance coverage. Before the implementation of the ACA, PLWH were at increased risk of being uninsured. In 2010, fewer than 1 in 5 PLWH had private insurance, compared with two-thirds of all Americans. About half of PLWH were enrolled in Medicaid or Medicare, and about a third were uninsured. In view of the positive correlation between survival rates for PLWH and insurance coverage, lack of insurance among PLWH is a serious concern. Uninsured PLWH are typically younger, have income levels at or below the federal poverty level (FPL), and are more likely to have been homeless in the last 12 months. The RWHAP has a pivotal role in addressing the major care needs of PLWH, including linking clients to care, reducing inequity in HIV risk and access to care, and addressing comorbidities.

### RWHAP Prior to the ACA

RWHAP was created by the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act of 1990. Its primary goals are to (a) reduce the use of costly inpatient care, (b) increase access to care for underserved populations, and (c) improve quality of life. One of few disease-specific programs, RWHAP is a safety network rather than a health insurance program. It is funded through a series of grant programs that are federally administered by the Health Services and Resources Administration (HRSA) HIV/AIDS Bureau to cities, states, territories, and public health districts. The funds are then distributed to regions and provider organizations to fund treatment and wrap-around services.

Among the strengths of the program is its provision of funds to HIV care facilities, which are typically more effective in treating PLWH than general clinics. In addition, the program funds a wide variety of services, including primary care, training programs for health care practitioners, assistance in identifying sources of care, access to medications, transportation to care sites, and provision of the necessary documentation to insurers and health care practitioners. AIDS Drug Assistance Programs (ADAPs) are a substantial component of the RWHAP, providing prescription medications to lower income, uninsured, and underinsured PLWH. In 2010, approximately one fourth of PLWH in the United States were enrolled in an ADAP, and ADAP funds accounted for 41% of the $1.93 billion in RWHAP spending in 2006.

Receiving RWHAP services has been consistently shown to be associated with better health outcomes. For uninsured and underinsured PLWH, assistance from the RWHAP has resulted in significantly higher use of ART (94% for those receiving RWHAP assistance versus 52% for those without) and virologic suppression (77% for those with assistance versus 39% without). Likewise, for insured PLWH, RWHAP assistance is associated with greater use of ART (96% for those with RWHAP assistance versus 90% for those without assistance) and higher rates of virologic suppression (81% for those with assistance versus 76% for those without), likely due to the provision of wrap-around and support services, including case management, which helps retain persons in medical care.

### The ACA and Its Expected Implications for PLWH

The ACA was signed into law in March 2010 (Public Law 111-148) with the goals of expanding medical insurance coverage, reforming the individual medical insurance market, reducing the rate of increases in health care spending, and improving the quality of clinical care. It was expected to have substantial implications for PLWH. An important goal of the ACA was to reduce the number of uninsured Americans, which was expected to benefit the many uninsured PLWH. In the private health insurance market, the ACA prohibits insurance companies from denying insurance due to preexisting conditions, including HIV infection. Allowing young adults to stay on their parents’ private insurance plans until they are 26 years old was expected to benefit some of the younger PLWH. Moreover, individuals with income between 100% and 400% of the FPL qualify for tax credits and subsidies for private insurance plans operated through the health insurance marketplace.

The ACA provides incentives to states to expand eligibility for Medicaid for their residents. Before the expansion, in many states individuals had to both fall below a threshold income and fit into a specific eligibility category, such as disability, having children, or being pregnant. Under the ACA’s Medicaid expansion, categorical eligibility requirements are eliminated and all Americans with incomes below 138% of the...
Non-Expansion adoption of the Medicaid expansion 19 states chose not to expand Medicaid Medicaid funding. without facing the penalty of losing all influence states to adopt the Medicaid states must have the option of deciding whether or not to expand Medicaid were too coercive and that Sebelius, however, the Supreme Court Federation of Independent Business v. FPL are eligible for Medicaid. In National Federation of Independent Business v. Sebelius, however, the Supreme Court ruled that the methods the Act used to influence states to adopt the Medicaid expansion were too coercive and that states must have the option of deciding whether or not to expand Medicaid without facing the penalty of losing all Medicaid funding. Given this choice, 19 states chose not to expand Medicaid eligibility. With high levels of health disparities, including among PLWH in many of these states, the uneven adoption of the Medicaid expansion was expected to increase health inequities among PLWH after ACA implementation
(Figure 1).

Scholars and policy makers expected that the combined effect of the expansion of Medicaid and the reformation of the private health insurance market would result in fewer PLWH having to wait until they were disabled to qualify for medical coverage, including ART. In addition to improving health outcomes, early access to ART prevents new infections. Earlier care is also associated with longer life expectancy and increased job productivity. Table 2 summarizes the main predictions by scholars and practitioners.

Expectations Regarding the ACA Impact on RWHAP Services

The ACA was predicted to decrease the number of uninsured people by 70% by eliminating annual limits and lifetime limits on health care coverage, which in turn was expected to reduce the number of uninsured and underinsured PLWH relying on RWHAP. Furthermore, increased access to ART was expected to result in cost savings to RWHAP ADAPs. For those PLWH who are dually eligible for Medicare and Medicaid, from 2012 through 2020 the ACA is incrementally reducing the gap between the ceiling at which Medicare stopped paying for 75% of drug costs and “catastrophic coverage.” These coverage gaps require certain PLWH to pay the full costs of prescription drugs until the onset of catastrophic coverage. Referred to as a “doughnut hole” in Medicare prescription drug plans, these gaps are expensive for PLWH, who can reach the ceiling quickly because of the high costs of ART. Specifically, ART alone of-ten costs more than $2500 per month, and the ceiling in 2010 for most Medicare Part D plans was $3610.

Before this provision of the ACA went into effect in 2012, ADAPs would take over paying the costs of medication once patients hit their ceiling, and because patients were not paying out-of-pocket, they would not reach the catastrophic spending level at which Medicare would again cover the costs for medication. Under the ACA, however, ADAP expenditures count toward out-of-pocket medication costs, thus individuals receiving ADAP benefits may reach the catastrophic spending level and Medicare funds may resume paying for medication. In addition, payments by ADAPs can now count toward true out-of-pocket medication costs. These 2 changes will shift some of the costs for covering medication from the RWHAP to Medicare.

Moreover, following ACA implementation, many states moved their ADAPs from a program that purchased medications to a program that purchased health insurance coverage. The Henry J. Kaiser Family Foundation concluded its report on ADAP by contrasting the
recent past of challenges that faced ADAP that led to the creation of waiting list, to the current state in which "emergency funding, increased rebates from manufacturers, and the implementation of the ACA have relieved much of this pressure." However, the impact of this “pressure relief” on PLWH was not examined. Moreover, this cost saving change was expected to result in reduced average cost per PLWH. In July 2017, National Alliance of State and Territorial AIDS Directors (NASTAD) related to these changes, stating that the increased financial resources can be used to provide services that increase virologic suppression by addressing structural and systemic barriers and staffing quality management programs. NASTAD has compiled a list of “best practices,” ideas and mechanisms used by states “to expand the range, quality, and effectiveness of services being offered through RWHAP Part B programs and/or ADAPs.” However, it is unknown to what degree these strategies are implemented by different states, and researchers did not examine how states are using the new funding sources and their impact on care and on patient-centered health outcomes.

The implementation of Patient-Centered Medical Homes (PCMHs) is another aspect of the ACA that was expected to improve health outcomes for PLWH. PCMHs increase retention in care and medication adherence, 2 factors that are crucial to improving health outcomes for PLWH.2 The National HIV/AIDS Strategy and the ACA positioned the PCMH as important strategy in improving quality of care and cost containment, and scholars therefore expected the ACA to increase use of PCMH. However, only 1 study examined PCMH for PLWH following ACA. The pilot study utilized interviews with key informants who shared positive experiences, and the authors called for studies employing stronger evidence.59

**Limitations of the ACA for PLWH**

The ACA may also have limitations. First, it categorically excludes legal immigrants from Medicaid eligibility for a 5-year waiting period, and it excludes undocumented immigrants entirely. Second, scholars expressed a concern that the increase in health care benefits may result in an overwhelming increase in demand on the health care workforce, particularly safety net providers. In addition, although access to insurance will increase for individuals in states that have expanded Medicaid, HIV disparities will grow due to the continued lack of insurance among PLWH in non-expansion states. Finally, as much of the funding for RWHAP relies on uncertain funding levels, scholars and advocates called for acknowledging the importance of the unique services the program provides, such as wrap-around services and medical case-management. RWHAP health care and social services practitioners surveyed and interviewed prior to ACA implementation highlighted the importance and effectiveness of the wrap-around services provided by RWHAP and expressed concern about lower reimbursement rates under the low-income health plans and Medicaid expansion, which could affect the solvency and availability of HIV practitioners. A related concern they shared was the quality of care PLWH might receive from primary care providers without HIV expertise.

**Experiences from Previous State-Based Health Policy Reforms**

In addition to predictions regarding the impact of ACA on RWHAP and its clients, indirect evidence about the effects of systemic changes in insurance provision is available from states that attempted near universal coverage prior to implementation of the ACA. Nearly a decade before the ACA began, Massachusetts began moving toward near universal health care coverage, which both improved outcomes (including rates of retention in care and viral load suppression) and access to insurance for PLWH. Even with near universal coverage, however, RWHAP funds remained an essential source of funding and were increasingly used to pay for insurance premiums and copayments in order to ensure retention in care. Similarly, in California, although 53% of individuals who were receiving services through a RWHAP transitioned to a low-income health program from January 2011 to June 2012, the number of individuals receiving care through the RWHAP increased slightly. Sixteen out of 18 agencies that provided services under the RWHAP, including case management, continued to do so to clients who transitioned into the low-income health programs. In addition, substance abuse treatment was not available through the low-income health plans, and thus PLWH continued to rely on RWHAP practitioners for those essential services. Before the 2014 ACA implementation, RWHAP practitioners strongly supported the need for the program in the post-ACA environment. Services for undocumented immigrants with HIV infection, PLWH who reside in states that did not expand Medicaid, and the need for wraparound services, especially case management, were noted as major reasons for the need for RWHAP post-ACA.

In sum, these early observations clearly demonstrated the important role that the RWHAP was expected to play in the new healthcare landscape. However, concerns were raised about its funding level and political support, especially as Congressional decision is needed for appropriation of RWHAP funding. In light of the concerns and hopes that preceded the ACA implementation as described here, it is important to explore the evidence on the impact of the ACA on the program and its clients, as well as on the role of RWHAP following the 2014 full roll out of the reform. The following section describes this evidence.

**Empirical Evidence: Early Observations of the Effect of the ACA on RWHAP and its Clients**

Early reports on the impact of the ACA on the general population revealed that it has largely increased the number of insured Americans by approximately 16.4 million, consisting of those who were previously uninsured and gained coverage due to the longer eligibility
for youth to remain on their parents’ plans, the Medicaid expansion, and marketplace options. RWHAP-related information after the ACA is available through the grey literature, ie, government and non-for profit organizations (Table 1). Some data are now available on the effects of the ACA on HIV care. In a study that compared compensated and RWHAP or uncompensated care in Medicaid expansion versus non-expansion state sites, half of PLWH relying on RWHAP or uncompensated care shifted to Medicaid in the first months of 2014 in expansion state sites. In contrast, reliance on the program and uncompensated care remained constant in non-expansion state sites. The researchers concluded that “[i]n the first half of 2014, the ACA did not eliminate the need for RWHAP safety net provider visit.” In an editorial commentary, the authors noted that the study included data for the first 6 months of 2014, at a time when many PLWH were still struggling to enroll in the ACA. Emerging evidence suggests a positive impact of the ACA on clients’ health outcomes. Analysis of RWHAP supplementary service provision after the ACA revealed that almost half of the clients in the Southeast sample received RWHAP supplementary services. Receipt of these services was associated with increased odds of viral suppression and of 2 measures of retention in care. Other researchers focus on specific aspects of HIV care and health outcomes that are relevant to RWHAP. Hellinger reported that the availability of insurance in 4 states dramatically reduced hospitalizations among PLWH. The analysis of hospital discharge data from 2012 through the June 2014 in 4 states that expanded Medicaid and 2 that did not revealed that hospitalizations of uninsured PLWH fell from 13.7% to 5.5% in the 4 Medicaid expansion states. In contrast, this percentage rose from 14.5% to 15.7% in the 2 nonexpansion states. Moreover, uninsured PLWH were 40% more likely to die in the hospital than those with insurance coverage.

In a study conducted in Virginia, authors examined receipt of RWHAP core medical, support, and insurance or direct medication assistance through ADAP. Of PLWH who engaged in any HIV care in 2014, 58% received any RWHAP service and 17% received all 3 types of services (comprehensive assistance). Receiving more classes of RWAH services was associated with improved HIV outcomes as evidenced by retention in care and viral suppression. The authors concluded that the program’s services were still required for optimal health outcomes of many PLWH.

Even after implementation of the ACA, however, out-of-pocket costs for ART remained high for PLWH insured by marketplace plans. The monthly out-of-pocket costs for HIV medications offered by the top 12 insurance companies extending Qualified Health Plans on Michigan’s Health Insurance Marketplace Exchange ranged from $12 to $667 per medication. Three Marketplace insurance plans placed all 31 assessed medications on the highest cost-sharing tier and charged 50% copayments for the medication. The researcher concluded that the high cost of coinsurance may discourage low-income PLWH from taking advantage of the ACA and may act as a barrier to medicine adherence.

Government reports provide some promising results as well. For instance, one fifth (20.6%) of RWHAP clients had no health care coverage in 2016, a decrease from 27.6% in 2012. These national reports, although demonstrating encouraging results, should be interpreted cautiously given limitations of data and measurements. Most notably, in the absence of national data, reports based on RWHAP client data are based only on clients who were enrolled in care. For others, it is unknown whether they dropped out of care or are seeing non-RWHAP providers.

Moreover, geographical differences remain largely undereexplored. For example, whereas few changes were observed in retention in care nationally, New Mexico saw a drop from 81% (n = 1279) in 2015 to 60% (n = 766) of RWHAP clients retained in care. Such local changes highlight the importance of understanding and addressing national trends, as well as geographic-
Continuing Need for RWHAP After the ACA

Despite the ACA’s expansive provisions, including those aimed at insuring millions more Americans, PLWH may still not be able to afford all of the costs of medication and treatment, or even to become or remain uninsured. Approximately 43% of PLWH live in states that did not expand Medicaid to all individuals making less than 138% of the FPL,10 thus many remain uninsured. Non-expansion states are typically in the South. These states also account for a substantial proportion of all HIV cases and for a growing proportion of new infections. HIV care infrastructure and access in Southern states were already the weakest prior to ACA implementation.10 Consequently, these states experience the biggest burden, but have the fewest resources given the lack of Medicaid expansion. Furthermore, many immigrants remain ineligible for Medicaid coverage.17 For these uninsured populations, the RWHAP may be the only source of HIV care, thus the need remains for the RWHAP safety-net function.

In addition, some individuals have fluctuating income near the FPL, which may result in a phenomenon called “churning.” Churning refers to involuntary changes in individuals’ insurance.2 Churning occurs when an individual is sometimes eligible for Medicaid (ie, making less than 138% of the FPL) and at other times ineligible (making more than 138% of the FPL) and thus required to purchase insurance through a state exchange.35 These changes in insurance coverage may result in interruption of care, but the RWHAP could ensure continuity of coverage by covering the costs of medical visits and medications during transition phases.35 Furthermore, it may be prudent to use the RWHAP funds to help pay premiums for those PLWH who are unable to do so entirely on their own.10

The RWHAP is also essential for covering medication copayments and services not covered by Medicaid or private insurance plans. Given the high cost of HIV medication, without contributions toward copayments from the RWHAP, PLWH may still be unable to afford medications.9,52 Furthermore, the health outcome benefits of wrap-around services, including housing assistance and transportation to health care, have been well documented. The ACA does not cover wrap-around services. The RWHAP can cover the deductibles and copayments for PLWH on marketplace private insurance plans, which may otherwise be unaffordable.17 The RWHAP can also assist with case management and assistance in obtaining other benefits.21 Considering administrative services, RWHAP care coordinators are likely to play a continuing and major role in enrolling low-income PLWH in insurance programs or Medicaid.17

The ACA provides preventive free care with no copay, including free HIV testing. This provision was expected to uncover over 2,500 new HIV cases by 2017.2 Combined with the effect of new recommendations to begin ART as soon as possible after diagnosis, there will be additional demand for ART and wrap-around services. This will place additional demand on the RWHAP, which is the only source of assistance for wrap-around services and which will be particularly important for providing ART to low income PLWH in states that have not expanded Medicaid.17

In summary, although the ACA is likely to substantially increase health care coverage and improve health outcomes for PLWH, numerous provisions of the RWHAP remain crucial for this population. As the number of PLWH in the United States is projected to increase by at least 24% over the next decade, increased funding for the RWHAP may be necessary to meet the demand for services.11 The adaptability of the RWHAP, which has been pivotal in its success in ensuring care for PLWH, is expected again to be vital in meeting the changing care needs of PLWH under the ACA. “The welcome expansion of insurance under the ACA is complementary to, not a substitute for, the care completion services historically delivered by the RWHAP.”42 The RWHAP will play an indispensable role in allowing PLWH “to take full advantage of the increased access made newly available by the ACA,” and thereby increase their lifespans, increase their quality of life, increase their productivity, and reduce transmission and incidence of HIV.42

Conclusions

Research and Practice Implications.

The importance of RWHAP to health outcomes of PLWH was well documented before the ACA implementation.1 In the time since the 2014 full ACA implementation, studies examined the degree to which care was compensated or not,47 and more recently the outcomes of RWHAP clients post-ACA.49 Most studies that examined the impact of the ACA on PLWH did not focus on RWHAP specifically or collect data before the 2014 full ACA implementation.53 Therefore, the claims regarding the impact of the ACA on health outcomes of RWHAP clients or former clients need further substantiation. Research should explore, using national data, the impact of ACA on RWHAP and non-RWHAP clients, with a focus on those who experienced changes to their medical insurance coverage following the establishment of the ACA. Moreover, research should focus on specific groups of PLWH that are at increased risk of being underserved, such as undocumented immigrants, transgender women, homeless individuals, and those with mental health issues. In addition, research should explore the impact of the ACA of RWHAP staff, examining implementation strategies,41 professional strategies and personal adjusting to ACA, as well as possible burnout that may lead to a reduction in HIV work force.

Following lingering gaps in HIV care, the 3 central dimensions to examine in future research on RWHAP post-ACA relate to linkage to care, inequity in access to care, and comorbidities. Studies are needed to explore the role of
### Table 2. Summary of Main Pre–Patient Protection and Affordable Care Act (ACA) Prediction and Post-ACA Impact Regarding the Ryan White HIV/AIDS Program (RWHAP)

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of article or analysis and primary subject or variables</th>
<th>Main Conclusions</th>
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<tbody>
<tr>
<td><strong>Sample Pre-ACA Implementation Articles Predicting ACA Impact on RWHAP</strong></td>
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</tbody>
</table>
| Martin, 2012<sup>25</sup> | Nonempirical
ACA impact on HIV clinical care | • RWHAP future is uncertain. Funded through annual appropriations, it may be more vulnerable to budget cuts or elimination
• The program will continue to fill insurance coverage gaps, and support provision of care by HIV specialists
• Predicted a shift from directly funding clinical care to funding wrap-around insurance |
| Abara, 2014<sup>2</sup> | Nonempirical
ACA and low income people living with HIV (PLWH) | • ACA will reduce the number of uninsured PLWH
• The number of PLWH relying on RWHAP will decrease.
• Cost savings were expected to AIDS Drug Assistance Program (ADAP)
• Exclusion of immigrants remains a concern |
| Cahill, 2015<sup>11</sup> | Nonempirical
RWHAP and ACA | • Access to insurance will increase for individuals in states that have expanded Medicaid
• HIV disparities will grow due to the continued lack of insurance among PLWH in non-expansion states
• Increased funding for the RWHAP may be necessary to meet the demand for services with projected growth in number of PLWH |
| Kates, 2013<sup>10</sup> | Nonempirical
ACA, PLWH, and RWHAP | • The ACA will expand coverage to PLWH
• RWHAP will still be needed to provide comprehensive, quality HIV care and to help engage and retain PLWH in care, as assistance with treatment adherence and case management are not typically covered by insurance plans |
| **Empirical Peer-Reviewed Articles Published Pre-ACA Full Implementation** | | |
| Hazleton, 2014<sup>41</sup> | Qualitative analysis
In-depth interviews with policymakers and clinicians concerning challenges and strategies to address changes accompanying health care expansion | • Clinicians highlighted the importance of RWHAP wrap-around services
• They expressed concern about solvency and availability of HIV clinicians and about the quality of care PLWH might receive from primary care practitioners without HIV expertise |
| Leibowitz, 2013<sup>42</sup> | Cross-sectional analysis of early evidence from California on transition to a reformed health insurance system for PLWH | • RWHAP practitioners highlighted the need to continue the program due to:
- The continued need for services for undocumented immigrants who are not covered under the ACA
- PLWH who reside in states that did not expand Medicaid and
- The need for wrap-around services, especially case management, that are unique to the program |
| Martin, 2013<sup>17</sup> | Qualitative analysis
In-depth interviews of ADAP service providers regarding changes anticipated with the ACA | • ADAP managers predicted that the focus of ADAP will change to "wrap-around services" including assistance of clients with out-of-pocket expenses
• Some expressed concerns about possible elimination of ADAP |
| Sood, 2014<sup>43</sup> | Mixed methods
Interviews with RWHAP practitioners to identify crucial components of RWHAP
Descriptive statistics regarding practitioner perceptions of quality and importance of RWHAP, value of components of RWHAP, and concerns | • RWHAP practitioners highlighted the need to continue the program due to:
- The continued need for services for undocumented immigrants who are not covered under the ACA
- PLWH who reside in states that did not expand Medicaid and
- The need for wrap-around services, especially case management, that are unique to the program |
| **Reports Published Post-ACA Full Implementation** | | |
| Health Resources and Services Administration (HRSA), 2017<sup>55</sup> | RWHAP annual client-level data | • One-fifth of RWHAP clients had no health care coverage in 2016, a decrease from 27.6% in 2012
• These national reports should be interpreted cautiously given data |
Table 2 (continued). Summary of Main Pre–Patient Protection and Affordable Care Act (ACA) Prediction and Post-ACA Impact Regrading the Ryan White HIV/AIDS Program (RWHAP)

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of article or analysis and primary subject or variables</th>
<th>Main Conclusions</th>
</tr>
</thead>
</table>
| Kaiser Family Foundation, 2017 | Analysis of the Centers for Disease Control and Prevention (CDC) data of national estimates of changes in insurance coverage among PLWH since the ACA implementation | • States changed their ADAPs’ focus from purchasing medications to purchasing health insurance coverage and emergency funding  
• Increased rebates from manufacturers and the ACA have relieved much of the financial pressure on the program, and this cost saving change was expected to result in reduced average cost per PLWH  
• However, the impact of this change was not examined |
| National Alliance of State and Territorial AIDS Directors (NASTAD) | Compilation “of ideas and mechanisms currently employed by states” - no specific methods listed | • The increased financial resources following reduced costs to RWHAP can be used to provide services that address structural/systemic barriers and staffing quality management programs  
• The authors provided a list of “best practices” used by states “to expand the range, quality, and effectiveness RWHAP Part B programs or ADAPs  
• However, the degree to which these strategies are implemented, how states are using the new funding sources, and their impact on care and on patient-centered health outcomes remain unknown |

RWHAP post-ACA in linking PLWH to care at diagnosis, retention in care, and adherence to treatment. These future studies should include health outcomes, including virologic suppression among PLWH who experienced changes following ACA, mortality and morbidity, and prevention of further transmission.

Moreover, future research should focus on specific populations and known inequities in HIV care and risk of HIV infection. As previously discussed, it is important to explore the effect of post-ACA changes to care on vulnerable, at-risk populations including ethnic and racial minorities, young adults, sexual minorities, and low-income PLWH. Similarly, future studies should explore the impact of ACA on current or former RWHAP clients with comorbidities. For example, what is the current level of access to mental health services among PLWH in general, and particularly among the third of PLWH with serious mental health or substance use disorders? What are the utilization, quality of care, and health outcomes among PLWH with cardiovascular disease, chronic kidney disease, or other age-associated comorbidities?

Future studies should also focus on PLWH’s ability to navigate the current system, as well as the ability of RWHAP staff, such as case managers, to facilitate this navigation. Studies conducted before ACA implementation documented that PLWH who were medically insured had higher survival rates than those who were uninsured. Therefore, future research should explore whether the increased coverage under the ACA led to an increase in longevity among the newly insured, and whether this led to decrease in inequities in health outcomes among specific demographic groups such as younger PLWH. Similarly, whereas in this review we considered the implications of the ACA to PLWH who receive RWHAP care, examination of the effects on new infections and HIV prevention efforts should also be carried out.

Policy Implications

In view of the evidence regarding the importance of the RWHAP as a safety net for PLWH, despite ACA implementation, which include specific association with viral suppression, retention in care, and prevention of transmission, policy makers should maintain support for RWHAP programs. Whereas some also expect cost savings, it is important to use this opportunity for providing
additional needed services for vulnerable populations. While RWHAP is maintained, policy makers should also commission a comprehensive cost analysis of the combined benefits of ACA and RWHAP to examine the long-term economic implications. If there are cost savings, it will be important for practitioners to leverage savings to enhance health services and outcomes with policy makers ensuring such gains are realized.

Community advocates, activists, and practitioners need to remain active in arguing for the merits of RWHAP-provided wrap around services for vulnerable subgroups. It is important to engage in advocacy and education to prevent the elimination of these services in short-sighted efforts to reduce costs. Cost-saving calculations often fail to take public health benefits into consideration, incorrectly viewing RWHAP as a form of health insurance rather than the public health program that it is. In the era of “treatment as prevention” and “U=U” (“undetectable = untransmittable”), where national HIV incidence is finally decreasing, it is crucial that we present evidence of the individual health improvements and the reduction in HIV transmission as ongoing benefits of RWHAP in the post-ACA era.

Financial affiliations in the past 12 months: Dr Ginozard has no relevant financial affiliations to disclose. Dr Oetzel has no relevant financial affiliations to disclose. Ms Van Meter has no relevant financial affiliations to disclose. Mr Gans has no relevant financial affiliations to disclose. Dr Gallant is employed by Gilead Sciences, Inc.

References

Review

HIV and the Liver

Kenneth E. Sherman, MD, PhD; Marion G. Peters, MD; David L. Thomas, MD, MPH

Among individuals with HIV infection, liver disease remains an important cause of morbidity and mortality, even with the availability of agents that cure hepatitis C infection and suppress hepatitis B replication. The causes of liver disease are multifaceted and continue to evolve as the population ages and new etiologies arise. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis and hepatitis viruses such as A, D, and E have emerged even as hepatitis C has receded. Newer antiretroviral agents may increase risk of weight gain and subsequent fatty infiltration, and prior use of nucleotide-based therapies may continue to impact liver health. Several barriers including economics, social stigma, and psychiatric disease impact identification of liver disease, as well as management and treatment interventions. Hepatocellular carcinoma is emerging as a more common and late-diagnosed complication in those with HIV infection and liver disease.

Keywords: HIV, hepatitis, NAFLD, NASH, ART, liver, antiretroviral therapy, hepatocellular carcinoma

Introduction

Over the last 2 decades we have gained a growing appreciation of the central role of liver disease in the course and outcomes of those with HIV infection. During this time we have witnessed a clear evolution with regard to the leading causes of liver disease and the management of those processes in individuals with HIV infection. The introduction of effective antiretroviral therapy (ART) in 1996 opened the door to longer life expectancies that permitted the expression of the full natural history of various liver diseases, often with an accelerated course compared with immunocompetent individuals. An early focus on hepatitis B virus (HBV) infection and drug-associated liver toxicity was quickly overshadowed by the emergence of our understanding of the importance of hepatitis C virus (HCV) infection on liver disease progression to cirrhosis and liver cancer. The development of direct acting agents with the ability to eradicate HCV infection in most individuals including those with HIV infection led many to believe that liver disease was no longer a substantial clinical issue in the setting of HIV infection. However, liver disease continues to be a major component of morbidity and mortality in those with HIV infection. HBV infection has reemerged as an important contributor to liver disease. Although alcoholic and nonalcoholic fatty liver has become a leading cause of liver transplantation in immunocompetent persons, we have barely scratched the surface in terms of understanding the unique epidemiologic and biologic patterns and processes that contribute to fatty liver disease among immunosuppressed patients. Viral infections that were long minimized in terms of their importance such as hepatitis A, D, and E now appear to be important contributors to progressive liver disease in some populations.

Since 2006, the US National Institutes of Health and industry partners have supported a biennial symposium designed to provide input from various stakeholders, including those representing hepatology, infectious diseases, pharmacology, alcohol and drug abuse, and government regulatory bodies. The most recent iteration of this meeting was held in September 2018 in Moran, Wyoming. In an effort to define the cutting edge of knowledge within the field, experts from a variety of domains were challenged to provide up-to-date information in their topic area regarding issues central to the research agenda of the future. In this report we summarize the key findings of the meeting in an effort to provide a roadmap for the next several years of research in the area of HIV and liver disease.

Changing HIV Epidemiology

The last decade has witnessed major changes in the epidemiology and management of HIV infection in the United States and elsewhere. Overall rates of new HIV infection declined between 2008 and 2013, and the introduction of preexposure prophylaxis (PrEP) has helped to stabilize the incidence at under 40,000 new cases/year in the United States. New infections of HIV are highly concentrated in the southeastern United States (52%) as well as in small urban geographic pockets and East Coast and West Coast cities. Men who have sex with men (MSM) account for 68% of risk for new infection. On a proportionate basis, the highest risk of infection is among people of color including African-American men and women and Hispanic men. Added to this mix are now discrete outbreaks of HIV infection primarily associated with injection drug use among young people with opioid use disorder. This pattern of spread is best characterized by the outbreak in Scott County Indiana, a rural, mostly white population where multigenerational sharing of drug paraphernalia led to an epidemic
of both HIV and HCV infections. Predictive models of high-risk populations were developed by the US Centers for Disease Control and Prevention (CDC). Subsequent outbreaks in the Ohio River Valley and elsewhere have substantiated the fears of spread to other communities and populations structurally similar to the Scott County outbreak.

On a positive note, improvements in the HIV care cascade have been demonstrated over the last 2 to 3 years such that a much higher proportion of patients with HIV infection have been identified and appropriately linked to care resulting in higher proportions of viral suppression. The most recent data from the CDC reports that 86% of individuals with HIV infection have been diagnosed, and 51% of individuals with HIV infection have viral suppression below 200 copies/mL. Recent studies suggest that a “test and treat” strategy reduced time to suppression of HIV from 132 days to 56 days. This work remains to be validated in larger trials.

**Etiology of Liver Disease**

Substantive changes have also been observed in patterns of liver disease among individuals with HIV infection. Key categories of disease include viral hepatitis, fatty liver, drug-associated hepatotoxicity, and liver cancer.

**Viral Hepatitis**

**Hepatitis A.** In 2016, an outbreak of hepatitis A virus (HAV) infection was first described in the San Diego Metropolitan area. This epidemic was primarily associated with poor sanitation among homeless populations who had not previously been vaccinated nor exposed to hepatitis A virus (HAV). The transient nature of this population led to rapid spread with secondary epidemics occurring in numerous other cities. According to the CDC, since the new HAV infection outbreaks were first observed in 2016, more than 15,000 cases, 8500 (57%) hospitalizations, and 140 deaths due to HAV infection have been reported (Figure 1). Simultaneously, reports of acute HAV infection among MSM populations increased in urban populations in Europe and the United States. Many of those with HAV infection had HIV infection. Reports at this meeting and elsewhere suggest that a large portion of the population with HIV infection is either unvaccinated or has lost detectable antibody. Indeed, overall HAV vaccine coverage in the general population is abysmal with rates of under 10% reported for adults who are older than 19 years of age in the United States. However, vaccination or revaccination among individuals with HIV infection does appear to yield protective antibody response in more than 90% of those treated. Modeling studies demonstrate that herd immunity does not occur until antibody levels reach at least 70%. However, following an outbreak of HAV infection in France, MSM still appeared to have substantial infection risk despite achieving at least 70% antibody seroprevalence. Protective antibody titers following vaccination appear to be lower than in those who recover from natural HAV infection. The severity of acute liver disease among those with HIV infection appears to be high (ie, higher rates of coagulopathy) and anecdotal data suggests that a rare relapsing form of HAV infection may be more common.

**Hepatitis B and D.** The importance of HBV infection in the setting of HIV infection has been continuously underestimated and overshadowed relative to concerns about HCV infection since the mid-1990s. Despite this oversight, the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) study clearly demonstrates the importance of HBV infection as a contributor to overall morbidity and mortality in individuals with HIV infection. Similarly, a detailed analysis of patient outcomes in the Veterans Administration system also identifies hepatitis B as a major contributor to liver injury. Despite a plethora of guidelines that suggest that all patients with HIV infection be tested for HBV and appropriately vaccinated if not currently infected or previously exposed, many patients remain unprotected. Despite widespread use of ART active against HBV there appears to be continued unawareness of the presence of chronic HBV infection or the risk of new HBV infection in those with HIV infection.

There is increasing interest in the simplification of ART regimens, particularly in those that have had viral control on a triple drug-therapy regimen for several years. Simplification often involves reduction to a 2-drug regimen and a combination of dolutegravir with rilpivirine, and abacavir or lamivudine has been studied in clinical trials with some success. However, those studies excluded patients with chronic HBV infection. Failure to recognize previously suppressed HBV infection with transition to a regimen that does not have activity against HBV will lead to flares of hepatitis that can be severe or even fatal in those with preexisting hepatic fibrosis. There are anecdotal reports of simplification with removal of tenofovir leaving lamivudine or emtricitabine as the only hepatitis B active agent. Patients with chronic HBV infection who are on such a regimen are at high risk of the emergence of resistant virus with HBV breakthrough due to
the presence of tyrosine-methionine-aspartic acid-aspartic acid (YMDD) motif mutations. The use of vaccine for prevention remains underappreciated. Even when HBV vaccination is administered, it is often ineffective (Figure 2). Systematic reviews of vaccine responsiveness yield a wide range of results with protective efficacy defined as greater than 10 million IU/mL occurring in 20% to 70% of vaccine recipients.17 Several studies have examined vaccination strategies to try and improve response rates.18-21

Hepatitis D virus (HDV) infection occurs as either a superinfection or coinfection with HBV infection. In Europe the frequency of HDV among patients with HBV/HIV coinfection is relatively high. A EuroSIDA collaboration reported that 14.5% of patients with HIV infection and chronic HBV infection were anti-HDV positive.22 Indeed, screening guidelines call for routine testing for HDV among all HBV-surface antigen-positive patients. In the United States the frequency of HDV infection is lower and routine testing has not been performed. Epidemiologic studies in Northern California have suggested that rates of as high as 8% may be seen in individuals with chronic HBV infection.23 However, exceedingly low rates of screening and lack of availability of HDV RNA testing probably lead to marked underestimation of the disease burden.24 Studies from Spain and elsewhere suggest that HDV/HBV/HIV coinfection is associated with more rapid progression of liver disease and increased rates of hepatocellular carcinoma (HCC).25


Hepatitis C. The overall prevalence of HCV infection among individuals with HIV infection has been well-established for several years. In many HIV cohorts in the United States and Europe, a blended composite antibody prevalence of 20% to 25% has been described (Figure 3). Though guidelines have suggested HCV testing in all individuals with HIV infection since 1999, HCV screening and surveillance is suboptimal. A recent study in Italy in those who were newly diagnosed with HIV infection found that 58% were unaware that they also had HCV infection.26 People who inject drugs have fragmented care and do not have substantial political voices. Many jurisdictions lack resources to measure burden by surveillance because HCV research is underfunded. In many states, systems are designed to restrict access to HCV direct-acting antivirals (DAAs) for people who inject drugs including restrictions on sobriety, fibrosis presence, and specialist access. This is in spite of evidence that 1) people who inject drugs respond equally well to HCV therapy with excellent adherence;27,28 2) high coverage with needle syringe programs and opioid substitution therapy reduces the incidence of HCV transmission by 74%,29 and 3) treatment without restrictions on HCV has markedly decreased new HCV infections.30 Presence of HCV RNA is highly associated with progression of fibrotic disease leading to cirrhosis and liver cancer. Many, though not all, studies suggest that HIV suppression significantly reduces rates of hepatic fibrosis but does not eliminate hepatic decompensation among those advanced disease.34,35 The availability of all-oral DAA regimens that were tolerable and highly efficacious among those with HIV infection opened the door to eradication efforts in the HIV-infected population. Although carefully conducted clinical trials suggest that there is no difference in overall treatment response compared to individuals without HIV infection, some, though not all, real-world studies continue to describe some decrement in sustained viral response rates or improvement in health-related quality of life.36-38 Effective therapy appears to halt injury and fibrotic progression and reduce the risk of HCC. The epidemiologic linkage between exposure to HCV and HIV in areas most affected by the opioid epidemic appears to be substantial, with HCV infection typically occurring first, followed by later introduction of HIV infection into closed population groups. Modeling data suggests that a combination of needle exchange services, opioid substitution therapy, and other addiction services combined with active treatment of HCV infection represents the best approach to blunt this epidemic.39 Other modalities may be needed in high-risk MSM populations.

Hepatitis E. The prevalence and significance of hepatitis E virus (HEV) infection among individuals with HIV infection remains controversial. In the United States, rates of exposure among those with HIV infection appear to be similar or perhaps slightly higher than the age-specific prevalence in the general population.40 Rates of exposure to this zoonotic disease primarily representing genotype 3 infection are high in both the immunocompetent and HIV-infected populations in some regions of Spain and France.41,42 Persistent chronic infections are reported more frequently in those areas that
have been observed in the United States in HIV-infected and in immunosuppressed solid organ transplant populations.\textsuperscript{43-45} It is possible that underreporting of HEV infection is a common phenomenon. The causes of this are multifactorial and include low rates of testing, lack of availability of testing facilities, lack of US Food and Drug Administration (FDA) approved assays, and possibly immunosuppression-associated seroconversion failure or seroreversion. Loss of antibody was observed in 40% of HIV-infected solid organ transplant recipients.\textsuperscript{46} Overall prevalence of HEV infection in the United States appears to be decreasing, which may be related to changes in behavioral patterns including increased use of processed meats and decreased direct animal exposure by the general population in recent decades. In contrast, some population groups in southern Europe continue to consume high levels of cold smoked sausage derived from pig liver (figatella), which appears to harbor a high risk of acute HEV infection.\textsuperscript{47}

### Fatty Liver

As HCV infection recedes in importance due to the availability of curative therapies, fatty liver disease in all of its forms and manifestations has become recognized as an increasingly important etiology of liver disease in individuals with HIV infection. Fatty liver disease can be broadly divided into alcoholic and nonalcoholic steatosis. Steatosis associated with alcohol use is a direct and expected outcome of alcohol oxidation within the liver. The amount of alcohol necessary to cause steatosis and the consequences of persistent steatosis with inflammation and oxidative injury (alcohol-associated liver disease) is not clearly defined. If one defines hazardous drinking behavior as greater than 14 drink equivalents per week for men and half that for a woman, then 10% of study participants in the Johns Hopkins HIV Clinical cohort of 6000 adults with HIV infection met that definition.\textsuperscript{48}

Clinical trials in patients with nonalcoholic steatohepatitis (NASH) often exclude subjects having more than 21 drinks per week for men or 14 drinks per week for women, but in the individual patient it is difficult to define the exact amount of alcohol consumption that may be associated with liver injury due to hepatic steatosis. Gene polymorphisms such as PNPLA3, overall nutritional status, and oxidative stress from other etiologies may all contribute to individual responses. Patients with HIV infection are more likely to have metabolic syndrome than those without HIV infection, even if they do not have higher body mass index.\textsuperscript{49}

When alcohol is not implicated as the causative etiology, the presence of steatosis in the liver implies the presence of nonalcoholic fatty liver disease (NAFLD). A subset of individuals with this condition have NASH, which is associated with progressive fibrosis leading to cirrhosis. In the setting of HIV infection, the exact prevalence of NAFLD and NASH remain uncertain. This is due in part to variation in the modalities used to define the presence of liver disease. Most commonly, fatty
liver is suggested by the presence of increased echogenicity on ultrasound. However, ultrasound is not specific for fat, and the presence of fat does not imply the presence of fibrosis or inflammation. Among patients with HIV infection, estimates of NAFLD prevalence determined by transient elastography ranges from 30% to 40%. Higher rates have been described when histologic criteria from liver biopsy are applied. Although obesity appears to be a primary driver for NAFLD in the general population and among individuals with HIV infection, a complex mix of factors may be present including metabolic syndrome and other factors may be involved. Recently, there is a suggestion that persons on integrase strand transfer inhibitor–based regimens may exhibit more weight gain, but it is not known if this is associated with an increased risk of fatty liver. NASH may be more frequent and more severe in those with HIV infection than those without HIV infection.

**Hepatocellular Carcinoma**

Over the last decade, HCC prevalence has increased among those with HIV infection. In a US Veteran’s Administration cohort of 24,000 individuals with HIV infection, the year 2003 represented a nadir with increased HCC rates observed in most subsequent years (Figure 4). Most of this was associated with HCV/HIV coinfection. Prevalence increases of 11% /year have been described in a multicohort consolidated analysis. HCC risk was associated with lower CD4+ count but not CD4+ count nadir. Interestingly, control of HIV replication does not seem to substantially reduce risk of cancer development.

**Mechanisms of Liver Injury**

HIV infection is associated with an increased risk of cirrhosis in individuals with chronic HCV and HBV infections, alcohol-related hepatitis, and possibly NAFLD. The risk of liver disease in individuals with HIV infection may be higher due to greater exposure to hepatotoxins such as alcohol and some older ART drugs. In addition, there are numerous mechanisms through which HIV could potentiate liver disease pathogenesis, including 1) direct effects of HIV on hepatocytes, stellate cells, or Kupffer cells; 2) increasing translocation of an altered gut microbiome into portal blood; or 3) depletion of CD4+ lymphocytes and widespread derangement of other immune responses. Although relevant animal models are lacking, in vitro studies have already revealed key insights into how HIV might potentiate the pathogenesis of HCV infection.

HCV infects hepatocytes where reactive oxygen species (ROS) accumulate and upregulate transcription of transforming growth factor beta-1 (TGFβ1) through a nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway. TGFβ1 stimulates stellate cells to produce the extracellular matrix that accumulates in cirrhosis. HIV cannot infect hepatocytes. However, the HIV envelope interacts with hepatocytes promoting ROS accumulation, and HIV may infect hepatic stellate cells. Both interactions potentiate the pro-fibrogenic pathways, enhancing TGFβ1 production in hepatocytes and production of the extracellular matrix by stellate cells. Although this model was originally established in immortalized hepatocyte or stellate cell lines, the Chung lab confirmed that HIV accentuates the profibrogenic effects of HCV using a more physiologic model coculturing hepatocytes (Huh 7.5.1 cells) and stellate cells (LX2).

Hepatic macrophages (Kupffer cells) also contribute to the pathogenesis of liver disease. HIV infects Kupffer cells and may disrupt Kupffer cell number or function. When activated, macrophages may stimulate stellate cells to produce extracellular matrix, a process that is represented by release of soluble CD163. HIV and HCV infection are each associated with elevated CD163 compared to controls, and levels are highest in individuals with HIV/HCV coinfection. CD163 levels correlate with hepatic inflammation and fibrosis in individuals with HIV/HCV coinfection. HIV infection is associated with increased translocation of microbial bacteria. Since nearly all portal blood drains through the liver, increased microbial translocation may alter the pathogenesis of liver disease either qualitatively (if the microbial components differ) or quantitatively (if there is more net translocation) to the liver. Several studies have reported a different intestinal microbiome in

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**Figure 4.** Prevalence of hepatocellular carcinoma (HCC) in the United States in individuals with HIV infection. (Used with permission from John Wiley and Sons). Solid lines represent actual prevalence. Dotted lines represent prevalence adjusted by direct standardization to age distribution of entire population from all calendar years.
individuals with HIV infection. However, at least some differences do appear to be confounded by alterations in the microbiome of MSM who are enriched in the HIV study population compared with heterosexual men and women versus being due to HIV infection itself.

Without regard for qualitative differences in the microbial contents, it is also possible that greater net translocation of bacteria promotes liver fibrogenesis. The association of HIV infection with elevated levels of blood correlates of microbial translocation like lipopolysaccharide or of Kupffer cell activation such as CD163 and soluble CD14 support that hypothesis. Further work is needed to clarify if there are consistent disruptions in the intestinal microbiome linked to HIV, if a “more favorable” microbiome can be established, and if that favorable microbiome alters disease phenotypes.

HIV infection may also affect HCV and HBV-induced chronic liver disease by altering immunity. Individuals with HIV infection have chronic immune-activation and altered type 1 interferon responses. Compared with persons with HCV infection alone, the CD8+ T cells from individuals with HIV/HCV coinfection are less potent and are more likely to express markers of exhaustion such as PD1 and CD39. PD-L1 levels appear to be present at higher levels in coinfection than in those with HVB monoinfection. Differences in the B cells and natural killer (NK) T cells of individuals with HIV/HCV coinfection have also been described.

Although there is comparatively more research on the pathogenesis of HIV-related liver disease in persons with chronic HCV infection, it is likely that some mechanisms contribute to other forms of liver disease. For example, increased microbial translocation, increases in hepatocyte ROS, and alterations in Kupffer cell physiology are mechanisms by which alcohol may promote liver fibrosis and steatosis (and are accentuated by HIV). Likewise, HIV-associated altered antiviral immunity would be expected to affect both HBV and HCV infections.

**Treatment and Barriers to Treatment of HBV and HCV**

There are substantial barriers to treatment of HBV and HCV infections, including low recognition of a largely silent disease as well as social and structural issues. Both viruses infrequently cause symptomatic disease so people do not seek medical care. Persons with HBV and HCV infections may suffer from stigma further precluding them from accessing care. Transmission is usually silent. Most people are asymptomatic or minimally symptomatic for years or decades. When they do access care, testing may not be performed or may be insufficient. The effects of fatigue and diminished quality of life may be attributed to other factors.

Men and women are equally represented in the acute HCV infection epidemic and many women only access care during pregnancy. Pregnancy is an opportunity to test and potentially treat in the third trimester. A recent small study showed a 100% sustained virologic response (SVR) rate without adverse fetal or maternal outcomes.

Individuals with HIV/HCV coinfection achieve the same rates of SVR as individuals with HCV monoinfection. The major concern with people with coinfection is drug-drug interactions that include some ART and common drugs such as statins and proton pump inhibitors. Before choosing an HCV regimen, careful assessment of current medications with potential HCV therapy is required using a pharmacist or online resources (www.hep-druginteractions.org; https://www.hcvguidelines.org/unique-populations/hiv-hcv).

HBV treatment in individuals with HIV infection is recommended for all patients with HIV/HBV coinfection, regardless of CD4+ cell count or need for HBV treatment. ART must include 2 drugs active against HBV, preferably tenofovir and emtricitabine, regardless of the level of HBV DNA. Such a regimen will reduce the likelihood of immune reconstitution inflammatory syndrome against HBV and reduce the risk of viral resistance that could occur with newer regimens without HBV active drugs or with lamivudine or emtricitabine alone. Treatment interruptions should be avoided as they can lead to serious life-threatening flares in HBV. Options to treat HBV alone are limited to interferons as all nucleos(t)ides have HIV activity. ART containing tenofovir-based therapy has been shown to prevent new HBV infection, in individuals with HIV infection for whom HBV vaccination failed.

**Management of Alcohol and Drug Use and Psychiatric Disorders in HIV**

Drug and alcohol dependence, often associated with mental illness, are important comorbidities that affect treatment outcomes and influence disease epidemiology and transmission. It is well established that mental illness increases risk of HIV infection and in a reciprocal manner, HIV increases risk for and severity of mental illnesses. Although HIV care practitioners can address many of their patients’ medically oriented health issues, they often have limited expertise in management of psychiatric disorders, which increase visit time and may overwhelm resources. Lyketsos and colleagues reported that 54% of patients entering an HIV primary care clinic setting had Axis I diagnoses including major depression (20%), adjustment disorder (18%), and cognitive impairment (18%) and that 74% were diagnosed with substance use disorder. Presence of depression was associated with discontinuation of ART, which led to decreased survival. Schizophrenia and bipolar disorders are also increased in those with HIV infection. HIV care practitioners can play a major role in HIV-infected with substance use populations disorders by 1) treating depression; 2) advocating for patient care in drug-treatment centers and 3) accepting that relapse is part of the disease process. Integrated care settings appear to provide better overall management of those with depression.

Substance disorder occurs in a complex overlay of social, psychiatric, and...
economic issues. For individuals with HIV infection who have coinfections with viral hepatitis, access to care can sometimes be difficult. As noted, many states restrict access of HCV DAAs for people who inject drugs. There are sobriety restrictions including marijuana use, for which there is no evidence that use affects treatment outcomes. Many jurisdictions have fibrosis restrictions, but those at the greatest risk of transmission often have low levels of hepatic fibrosis. A few insurers still mandate "one and done" policies that allow only one treatment for a disease with a relatively low but real reinfection risk rate. Current guidance (www.hcvguidelines.org) from the American Association for the Study of Liver Disease and Infectious Diseases Society of America suggest at least annual HCV RNA testing for people who inject drugs after HCV clearance (either spontaneous or through treatment). Simmons and colleagues provided evidence that individuals with HCV/HIV coinfection were at higher risk of reinfection and recurrence than other groups. Opioid agonist therapy has been shown to reduce incidence of HCV infection among people who inject drugs. Combined with needle syringe exchange programs, even greater reduction in transmission can be demonstrated. Even active injectors can be successfully treated for HCV infection.

Unhealthy alcohol use is another important cofactor in modulation of liver disease among individuals with HIV infection. It influences provision of HIV care, sexual risk behaviors, medical comorbidities, and mental health. Overall all-cause mortality among individuals with HIV infection is higher than in those without HIV infection in all categories of alcohol use/month. Despite this, alcohol use is not prioritized as a problem by either patients or health care practitioners, and few HIV practitioners report implementation of evidence-based alcohol-related care in their practices. Various modalities are available to modulate unhealthy alcohol use including medications (acamprosate, disulfiram, naltrexone) and counseling interventions (Motivational Enhancement Therapy, Cognitive Behavioral Therapy). In one study, drinking outcome measures were improved among women with HIV infection in just one series of 20-minute face-to-face intervention sessions. Similar results were reported by Kahler et al, using one 60-minute interview with follow-up phone calls and “booster” sessions. Adjunctive use of medications like naltrexone has been shown to be safe and effective in those with HIV infection.

Research Agenda: The Path Forward

Despite advances in the last several years, many key questions remain to be answered. With regard to HIV care, underserved, and unidentified populations remain difficult to access. Research into identifying and integrating these populations into care (implementation research) remains a crucial need. This has been highlighted by guidance from the CDC, National Institute of Allergy and Infectious Diseases, and US Department of Health and Human Services. Although ART regimens have evolved such that direct hepatic toxicity is reduced, concern regarding long-term and persistent effects of prior nucleoside-based therapies on the liver remains. Research into effects of exposure on hepatoportal sclerosis and development of portal hypertension will be important. This may be one factor into the observation that decompensation occurs at higher rates in those with HIV and liver disease even when underlying processes (eg, HCV infection) are treated. The mechanisms that underlie the observations remain to be elucidated. As our population with HIV infection ages, HCC occurrence is increasingly frequent and important. Are there optimal screening and surveillance strategies in those with HIV infection that differ from those without? Does risk remain in those with controlled (suppressed) HIV infection? There are few data regarding aging and the liver itself in the context of HIV infection. New pathways for liver injury and fibrosis continue to be identified. What role do immune defects that persist after HIV suppression play in these? It appears that the role of chemokines and chemokine blockade is emerging as an important feature of fibrosis. Much focus is on patients with NASH but there may be a role for chemokine receptor 5 (CCR5) blockade in those with abnormal liver tests without clear etiology for the liver disease. The microbiome remains largely unexplored within the HIV-infected population. Can it be manipulated? Indeed, do those with HIV infection differ from those not infected? Hepatic fibrosis remains the key endpoint for many disease pathways. Are there new markers of fibrosis and regression of fibrosis that need to be explored (eg, kynurenine)? With regard to HBV/HIV coinfection, prevention and cure remain elusive. Prevention is largely reliant on successful vaccination but outcomes are suboptimal in individuals with HIV infection. The reasons for this remain unknown. In a practical sense new strategies are needed to improve HBV vaccine outcomes. These may include use of toll-like receptor 9 (TLR9) or other agonists. With regard to functional cure, covalently closed circular (ccc) DNA clearance is essential. Experts remain divided on whether antiviral or immune approaches (or both) are needed. New biomarkers of cure are also needed and exploration of novel biomarkers like pre-genomic RNA have not yet been described in HIV-infected cohorts. Curing HBV infection prevents an emergence of HDV, but since that
will be difficult, better screening, new drugs, and new targets are needed. We do not know why HCC risk is increased when HDV infection is present in the setting of triple infection (HBV/HDV/HIV). Though many believe that HCV infection is no longer a problem because it can be cured, many questions remain. What are the long-term effects of care on hepatic fibrosis and HCC, as well as non-liver morbidities in those with HIV? Do recreational drugs affect DAA metabolism and effectiveness in real-world settings? Would long-term DAAs serve as PrEP in high-risk populations? Can we treat subgroups for even short durations? Does a vaccine make sense? If yes, how, who, and when? NAFLD/NASH appears to be on the rise in those with HIV infection and the population in general in the United States and elsewhere. Is there more steatosis in individuals with HIV infection? What factors related to HIV infection impact disease severity and progression? Do we need modification of non-invasive biomarkers in the context of HIV infection and its treatment? When will studies of new therapeutic agents enter the HIV-infected population? Liver and kidney transplantation in HIV are effective modalities but immunologic effects of protease inhibitors on rejection have raised questions. Is there an expanded role for rapamycin and does this have an impact on HIV reservoir? Why do less than 30% of transplant centers in the United States list patients with HIV infection and how do we change that? As centers use HCV- and HIV-positive organs to relieve the national organ shortage, how do we manage patients differently? The impact of substances of abuse on HIV care and management remains unclear. It appears that cocaine use facilitates HIV progression but the role in liver disease is less clear. Integrated treatment models for alcohol, opioids, and cocaine seem to work but are difficult to implement on a large-scale basis. What can we learn from other countries? Models have been developed that guide disease management but most remain to be tested in real-world settings. Psychiatric issues provide a barrier to many of the issues of liver disease in individuals with HIV infection. New economic models and ways to reduce stigma need to be explored, evaluated, and codified.

For the next 5 to 10 years, investigators across a variety of disciplines have an opportunity to answer these and other questions, which will lead to improved care and improved lives for those with HIV infection and liver disease.

Financial affiliations in the past 12 months: Dr Sherman has received grant support or contracts awarded to his institution from AbbVie, Gilead Sciences, Inc, Intercept Pharmaceuticals, Inc, MedImmune, and Merck & Co, Inc; and served as an advisor or consultant to UniQure and Inovio Pharmaceuticals; and served on data and safety monitoring boards for Watermark and Medpace. Dr Peters has served as an advisor to Abbott. Her spouse is employed by Hoffman-La Roche. Dr Thomas has no relevant financial affiliations to disclose.

Funding for this conference was made possible [in part] by the National Institutes of Health under Award Number 2R13AI071925-08. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the US Government. Also supported in part by educational grants from: Abbott Diagnostics, Dova Pharmaceuticals, Gilead Sciences, Inc., Janssen Therapeutics, LP, Salix, and ViIV Healthcare.

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Special Contribution

2019 Update of the Drug Resistance Mutations in HIV-1

Annemarie M. Wensing, MD, PhD; Vincent Calvez, MD, PhD; Francesca Ceccherini-Silberstein, PhD; Charlotte Charpentier, PharmD, PhD; Huldrych F. Günthard, MD; Roger Paredes, MD, PhD; Robert W. Shafer, MD; Douglas D. Richman, MD

The 2019 edition of the IAS–USA drug resistance mutations list updates the Figure last published in January 2017. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The Figure is designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs, and therefore, in making clinical decisions regarding antiretroviral therapy.

Keywords: HIV, antiretroviral, drug resistance, therapy, mutations

The 2019 edition of the International Antiviral Society–USA (IAS–USA) drug resistance mutations list updates the Figure last published in January 2017.1 In this update:

• 2 integrase strand transfer inhibitors (InSTIs), bictegravir and cabotegravir, and the nonnucleoside reverse transcriptase inhibitor (NNRTI), doravirine, were added to the Figure.

• Bictegravir (formerly GS-9883) was approved by the US Food and Drug Administration (FDA) in February 2018 as part of a fixed-dose combination of bictegravir/emtricitabine/tenofovir alafenamide for the treatment of HIV-infected, treatment-naive individuals or to replace an antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA below 50 copies/mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of the combination.2

• Doravirine (formerly MK-1439) was approved by the FDA in August 2018 for the treatment of HIV-infected, treatment-naive individuals in combination with other antiretroviral drugs.3

• Several changes were made to drugs already on the Figure. On the lopinavir/ritonavir bar, mutations at positions 50, 54, and 84 were changed to boldface to indicate recognition as major mutations rather than minor mutations.4 The G118R mutation was added to the bar for the InSTI dolutegravir.5,6

• For antiretroviral drugs that are no longer recommended, the bars are listed at the bottom of the class and are shaded in gray.

Methods

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on drug resistance–associated mutations for HIV clinical practitioners. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV-1. This list includes mutations that may contribute to a reduced virologic response to a drug.

The group considers only data that have been published or have been presented at a scientific conference. Table 1 provides the list of amino acids and the abbreviations used. Drugs that have been approved by the US Food and Drug Administration and are generally recommended, as well as any drugs

Table 1. Amino acids and their abbreviations.

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Dr Wensing (Group Chair), University Medical Center Utrecht, The Netherlands and University of the Witwatersrand, Johannesburg, South Africa; Dr Calvez, Pierre et Marie Curie University and Pitié-Salpêtrière Hospital, Paris, France; Dr Ceccherini-Silberstein, University of Rome Tor Vergata, Rome, Italy; Dr Charpentier, Paris Diderot University and Bichat-Claude Bernard Hospital, France; Dr Günthard, University Hospital Zurich and Institute of Medical Virology, University of Zurich, Switzerland; Dr Paredes, HIV Unit and IrsiCaixa AIDS Research Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; Dr Shafer, Stanford University Medical School, California; Dr Richman (Group Vice Chair), Veterans Affairs San Diego Healthcare System and University of California San Diego.
available in expanded access programs are included (listed in alphabetic order by drug class). Drugs that are no longer recommended are listed at the bottom of the class and are shaded in gray. User notes provide additional information. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

The magnitude of the reduction in susceptibility conferred by drug resistance mutations varies widely, and is modulated by the genetic context of the HIV sequence in which the mutation occurs. Despite the fact that mutations result in a spectrum of degrees of resistance, mutations have been arbitrarily designated as major (bolded) or minor (not bolded) (see Figure 1). Those defined as major tend to occur earlier during treatment failure and generally confer larger reductions in susceptibility. Those defined as minor tend to accrue after the emergence of a major mutation, confer some incremental resistance, may occur as well as polymorphisms in wild-type virus, and in some cases do not reduce susceptibility but restore replication fitness to viruses with resistance mutations that impair fitness. In general, a major mutation should raise concern that a drug is at least partially compromised; a minor mutation on its own may not raise such a concern, but it should add concern in the presence of other mutations.

Identification of Mutations

The mutations listed are those that have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from patients in whom the drug is failing; (4) association studies between genotype and phenotype response in patients exposed to the drug.

The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in otherwise wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance. Consequently, only some of the resistance mutations depicted on the Figure can be used to identify transmitted drug resistance.

Clinical Context

The Figure is designed for practitioners to use in identifying key mutations associated with antiretroviral drug resistance and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient’s history of antiretroviral therapy; (2) recognizing that in the absence of current drug treatment that is conferring selection pressure, resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of a first-line regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen. In this setting, resistance emerges most commonly to lamivudine or emtricitabine, nonnucleoside analogue reverse transcriptase inhibitors, or first generation InSTIs (elvitegravir, raltegravir).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, a prolonged interval between the time of antiretroviral drug discontinuation and genotypic testing, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

For more in-depth reading and an extensive reference list, see the 2018 IAS–USA panel recommendations for resistance testing and 2018 IAS–USA panel recommendations for antiretroviral therapy.

Reprint Requests

The Drug Resistance Mutations Group welcomes interest in the Figure as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the Figure and no alterations in format or content can be made.

Requests to reprint the material should include the name of the publisher or sponsor, the name or a description of the publication in which the material will be reprinted, the funding organization(s), if applicable, and the intended audience. Requests to make any minimal adaptations of the material should include the former, plus a detailed explanation of the adaptation(s) and, if possible, a copy of the

Comments

Please send your evidence-based comments, including relevant reference citations, to journal@iasusa.org.
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Permission will be granted only for requests to reprint or adapt the most current version of the Figure as they are posted at www.iasusa.org. Because scientific understanding of HIV drug resistance evolves and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact IAS–USA.

Financial affiliations in the past 12 months: Dr Calvez has served as an advisor or consultant to and has received research grants from Bristol-Myers Squibb, Johnson & Johnson, Viiv Healthcare, and Gilead Sciences, Inc, and is a founder of SkinDermic Pharma. Dr Ceccherini-Silberstein has been a consultant to Viiv Healthcare, Bristol-Myers Squibb, and Merck Sharp & Dohme, Inc, and has received research grants from Viiv Healthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc, and has received research grants from Viiv Healthcare. Dr Günthard has served as a consultant to Merck & Co, Inc, Viiv Healthcare, Sandoz, Teva Pharmaceuticals Industries, and Gilead Sciences, Inc, and has received research grants from Gilead Sciences, Inc. Dr Paredes has received research grants from and has served as an advisor for Viiv Healthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc. Dr Richman has been a consultant to Antiva Biosciences, Gilead Sciences, Inc, and Viriome, Inc. Dr Shaffer has received research grants from Janssen Therapeutics, Vela Diagnostics, and InSilixa, Inc, and consulting fees from Abbott Diagnostics. Dr Wensing has served on advisory boards for Viiv Healthcare, Merck & Co, Inc, Janssen Therapeutics, and Gilead Sciences, Inc, and has received research or unrestricted educational grants from Janssen Therapeutics, Viiv Healthcare, Merck & Co, Inc, and Gilead Sciences, Inc.

Funding/Support: This work was funded by IAS–USA. No commercial company or government funding was used to support the effort. Panel members are not compensated.

The authors thank Jose Francisco for administrative support for the work.

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# Mutations in the Reverse Transcriptase Gene Associated with Resistance to Reverse Transcriptase Inhibitors

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)

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151 Complex (affects all nRTIs currently approved by the US FDA)

## Thymidine Analogue-Associated Mutations

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## Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS (PIs) 15,16,17

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| 10 | 32 | 46 | 47 | 50 | 54 | 73 | 76 | 82 | 84 | 90 |
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| Nelfinavir21,22 | L | L | G | I | I | A | G | V | V | I | L |
|----------------|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 30 | 36 | 46 | 71 | 77 | 82 | 84 | 88 | 90 |
| N |
|   | I | L | L | L | V | M | S | T |

| Saquinavir/ ritonavir21 | L | L | G | I | I | A | G | V | V | I | L |
|-------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 24 | 48 | 54 | 62 | 71 | 73 | 77 | 82 | 84 | 90 |
| I | I | V | V | V | S | I | A | V | M |
| R | V | L | T | F | S | T | S |

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

| Enfuvirtide23 | G | I | V | Q | Q | Q | N | N | D | V | A | R | H | T | D | S | M | E |
| 36 | 37 | 38 | 39 | 40 | 42 | 43 |

| Maraviroc24 | See User Note |

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS25

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Mutations known to be selected by TAMs (ie, M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) also confer reduced susceptibility to all currently approved nRTIs except emtricitabine and lamivudine, which in fact reverse the magnitude of resistance and are recommended with tenofovir or zidovudine in the presence of TAMs. The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.21-24

5. Although reverse transcriptase changes associated with the E44D and V118I mutations may have an accessory role in increased resistance to nRTIs in the presence of TAMs, their clinical relevance is very limited.25-27

6. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo. When associated with TAMs, M184V increases abacavir resistance.28

7. The presence of K65R is associated with a reduced virologic response to tenofovir.4 A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.4 The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.29-31

8. The presence of M184V appears to delay or prevent emergence of TAMs.32 This effect may be overcome by an accumulation of TAMs or other mutations.

9. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients.33,34 The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.35

10. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E— is associated with resistance to didanosine.36 The presence of K70R or M184V alone does not decrease virologic response to didanosine.37 However, the mutations depicted on the Figure Bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

11. There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI resistance.38

12. Doravirine is active in vitro against variants containing the common NNRTI mutations K103N, E159R, Y181C, and G190A.39,40 Doravirine selects for mutations at positions 106, 108, 227, and 234, with more than 1 mutation usually required for substantial levels of resistance.41 Mutations V106A, Y188L, and M230L are associated with a 10- or greater fold reduced susceptibility to doravirine. V106A and Y188L have also been selected in vivo.42-45 In 1 clinical isolate, G190E was associated with about 20-fold reduced susceptibility to doravirine.40 Furthermore, the double and triple mutants V106A and F227L, V106A and L234I, V106A and F227L and L234I, and V106A and I90A and F227L, are all associated with substantial resistance to doravirine.39,41,44

13. Resistance to etravirine has been extensively studied only in the context of coadministration with ritonavir-boosted darunavir. There, mutations associated with virologic outcome were assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values were calculated, and assessments of genotypetypephenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.45-47 The single mutations L100I, K101P, and Y181C/I/V have high relative weights with regard to reduced susceptibility and reduced clinical response compared with other mutations.48,49 The presence of K103N alone does not affect etravirine response.49 Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.50-52

14. Fifteen mutations have been associated with decreased rilpivirine susceptibility (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H22Y, F227C, and M230I/L) 53-55 A 16th mutation, T188L, reduces rilpivirine susceptibility 6 fold. The K101P and Y181I/V mutations reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but are not commonly observed in patients receiving rilpivirine.56-58 Mutations at position 138 (most notably E138A) may occur as natural polymorphisms, especially in non-B subtype virus.59 The K101E, E138K, and Y181C mutations, each of which reduces rilpivirine susceptibility 2.5 fold to 5 fold, occur commonly in patients receiving rilpivirine. E138K and to a lesser extent K101E usually occur in combination with the nRTI resistance-associated mutation M184I, which alone does not reduce rilpivirine susceptibility. When M184I is combined with E138K or K101E, rilpivirine susceptibility is reduced about 7 fold and 4.5 fold, respectively.58,60-62 The combinations of reverse transcriptase-associated mutations L100I plus K103N/S and L100I plus K103R plus V179D were strongly associated with reduced susceptibility to rilpivirine. However, for isolates harboring the K103N/S or V179D as single mutations, no reduction in susceptibility was detected.55,63

15. Often, several mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).64

16. Mutations in Gag cleavage sites may confer or contribute to resistance to PIs and may even emerge before mutations in protease.65 A large proportion of virus samples from
patients with confirmed virologic failure on a PI-containing regimen is not found to have PI resistance–associated mutations.

17. Ritonavir is not listed separately, as it is currently used only at low doses as a pharmacologic booster of other PIs.

18. Several mutations are associated with atazanavir resistance. Their impacts differ, with 150I, 184V, and N88S having the greatest effect. Mutations that are selected during unboosted atazanavir are not different from those selected during boosted atazanavir, but the relative frequency of mutations may differ. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M46I plus L76V may increase susceptibility to atazanavir when no other related mutations are present.

19. Virologic response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI resistance–associated mutations. Reductions in response are associated with increasing numbers of the mutations indicated on the Figure Bar. The negative impact of the protease mutations I47V, I54M, T74P, and I84V and the positive impact of the protease mutation V82A on virologic response to ritonavir-boosted darunavir were shown independently in 2 data sets. Some of these mutations appear to have a greater effect on susceptibility than others, as I50V is associated with a clear impact on susceptibility. Mutations described in the N155H pathway include this major mutation plus one or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway are (1) a mutation at N155H, Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74I/M, E92Q, T97A, E92Q plus T97A, and I84V. These mutations are associated with a decreased virologic response to ritonavir-boosted darunavir.

20. Virologic response to ritonavir-boosted lopinavir is affected by the presence of 3 or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, I50V, I54L/M, T74P, L76V, I84V, or L89V was associated with a decreased virologic response to ritonavir-boosted lopinavir.

21. The mutations depicted on the Figure Bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

22. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI resistance–associated mutations.

23. Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the env (eg, the HR2 region or those yet to be identified), as well as coreceptor usage and density, may affect susceptibility to enfuvirtide.

24. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that use only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXC chemokine receptor 4 (CXCR4; termed dual/mixed [D/M] virus) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists. Virologic failure of these drugs is frequently associated with outgrowth of D/M or X4 virus from a preexisting minority population present at levels below the limit of assay detection. Mutations in HIV-1 gp120 that allow the virus to bind to the drug-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 after virologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism. There is no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted on the Figure Bar. Some CCR5 antagonist–resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3, the clinical significance of such mutations is not yet known.

25. In site-directed mutants and clinical isolates, the mutation F121Y has a profound effect on susceptibility to elvitegravir and raltegravir and to a lesser extent to dolutegravir. R263K can be selected in vivo during treatment with dolutegravir and raltegravir and results in a 2- to 5-fold reduction in susceptibility to elvitegravir, raltegravir, and cabotegravir. 263K has been selected in vitro under pressure with bictegravir and cabotegravir.

26. Bictegravir is a second-generation integrase strand transfer inhibitor (InSTI), like dolutegravir, with higher genetic barrier to resistance than raltegravir and elvitegravir. Bictegravir has only been studied in detail in elvitegravir susceptibility and may require additional mutations for resistance. The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.

27. Bictegravir is an investigational, long-acting InSTI. In clinical trials, Q148R (fold changes, 5.2-9.4) and G140R (fold change, 6.7) have been observed particularly in HIV-1 A1 subtype harboring the L74I integrase polymorphism. The G118R mutation has been selected in macaques receiving bictegravir (long-acting) for pre-exposure prophylaxis during acute simian/human immunodeficiency virus infection.

28. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir. Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses indicate that Q148H/R and G140S in combination with mutations L74I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5-fold to 20-fold reduced dolutegravir susceptibility and reduced virologic suppression in patients.

29. Seven elvitegravir codon mutations have been observed in InSTI treatment–naive and –experienced patients in whom therapy is failing. Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses indicate that Q148H/R and G140S in combination with mutations L74I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5-fold to 20-fold reduced dolutegravir susceptibility and reduced virologic suppression in patients.

30. Raltegravir failure is associated with integrase mutations in at least 3 distinct, but not exclusive, genetic pathways described by 2 or more mutations including (1) a mutation at Q148H/R/K, N155H, or Y143R/H/C, and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/R/K pathway include L74I/M, E92Q, T97A, E92Q plus T97A, Y143H, G163K/R, V151I, or D232N. The Y143R/H/C mutation is uncommon. E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (5 fold) cross-resistance to raltegravir. N155H mutants tend to predominate early in the course of raltegravir failure, but are gradually replaced by viruses with higher resistance, often bearing mutations G140S plus Q148H/R/K, with continuing raltegravir treatment.

References to the User Notes:
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UPCOMING ACTIVITIES

MARK YOUR CALENDAR FOR SPRING 2020: IAS–USA SCHEDULES HIV UPDATE COURSES

The International Antiviral Society–USA (IAS–USA) will present the latest important developments in the HIV prevention and management from the past year in its 2020 series of live regional courses, beginning March 19 in New York City.

These CME course are designed for HIV specialists actively involved in HIV disease management. Our faculty provided advanced-level presentations with balanced, timely, scientifically rigorous, and clinically relevant information about HIV treatment.

Below are 2020 dates and locations. More information will be announced soon.

New York, New York — Thursday, March 19      Los Angeles, California — Friday, May 1
Atlanta, Georgia — Friday, April 3             Washington, DC — Friday, May 8
San Francisco, California — Thursday, April 23 Chicago, Illinois — Thursday, May 21

(Tentative) Interactive Webinars

Live, interactive continuing medical education (CME) in the comfort of your home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for details. Upcoming webinars will cover the following topics:

Managing Syphilis in HIV Coinfected Patients: A Case Bases Approach — Tuesday, October 15, 2019
Presenter: Andrea L. Cox, MD

Management of Sexually Transmitted Infections Among Youth — Tuesday, October 29, 2019
Sharon Nachman, MD

PrEP Implementation: Populations, Providers, and Policies — Tuesday, November 19, 2019
Hyman Scott, MD, MPH

Prior webinars are available for CME credit for up to 1 year after the live broadcast. Visit the IAS–USA website for a full list of upcoming and archived webinars.

New Sexual Health, HIV Prevention, and Primary Care in 2019

This new, full-day, live CME course addressed the shift in primary responsibility for managing PrEP and STIs from HIV and infectious disease clinicians to primary care and internal medicine practitioners, and the best practices for maintaining the sexual health of those with or at risk for HIV infection.

Information will be presented by an expert faculty of STI and HIV/AIDS clinicians and researchers.

Visit the IAS–USA website to view a webcast of this course.

New York, New York — September 12, 2019
Chairs: Roy M. Gulick, MD, MPH; Jeanne M. Marrazzo, MD, MPH

Cases on the Web

A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for a full list of Cases on the Web activities.

Recent activities address the following topics:

HIV-2: Clinical Features, Diagnosis, and Management
Authors: Jacqueline T. Chu, MD; Rajesh T. Gandhi, MD
Date of Last Review: February 11, 2019
Expires: February 11, 2020
1.25 AMA PRA Category 1 Credits™ Available

Considerations in the Treatment of Opioid Use Disorder in Patients with HIV Infection and HCV Coinfection
Authors: Jennifer Edelman, MD, MHSc; Jeanette M. Tetault, MD

Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for email updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities.
Antiretroviral therapy (ART) should be started as soon as possible after HIV diagnosis. Recommended starting ART regimens in patients with any baseline viral load include bictegravir plus tenofovir alafenamide (TAF)/emtricitabine (FTC), dolutegravir (DTG) plus abacavir/lamivudine, DTG plus TAF (or TDF)/FTC, or DTG plus 3TC. Initial laboratory evaluation includes CD4+ cell count, plasma HIV-1 RNA, and testing for HIV reverse transcriptase and protease resistance mutations. ART regimens do not need to be altered for virologic blips due to release of virus from chronically latently infected cells in patients otherwise exhibiting viral suppression. Patients with continuously undetectable viral load on ART pose virtually no risk of transmitting infection through sexual contact. This article is based on a case-based presentation by Michael S. Saag, MD, at the 2018 Clinical Conference at the National Ryan White Conference on HIV Care & Treatment in December 2018 and intended for clinicians who are new to HIV disease management.

Keywords: HIV, antiretroviral, initial ART, InSTI, integrase inhibitor, nRTI, NNRTI, protease inhibitor, PI, viral load, CD4+ count, HIV RNA

Initial ART

Two important resources for use of antiretroviral therapy (ART) are the updated guidelines from the International Antiviral Society–USA (IAS–USA) and from the US Department of Health and Human Services (DHHS). The goal of therapy is to block HIV replication (Figure 1).

ART should be started as soon as possible after diagnosis of HIV infection. This includes rapid start on the day of diagnosis, unless the patient is not ready to commit to starting therapy. Further, ART should be started as soon as possible (but within 2 weeks) after diagnosis of most HIV-related opportunistic diseases. The objective of starting as soon as possible is to effectively suppress the virus, which reduces immunologic damage in the patient and reduces likelihood of forward transmission (Figure 1). Less time between diagnosis and the initiation ART also increases the likelihood that patients will show up for their first clinic visit to initiate treatment.

Structural barriers to initiating ART and HIV care should be removed. Before starting ART, laboratory monitoring should include: CD4+ cell count; plasma HIV-1 RNA; hepatitis A, B, and C virus serologies; serum chemistries; estimated creatinine clearance rate; complete blood cell count; urine glucose and protein; sexually transmitted infection (STI) screening; and fasting lipid levels. In regions with an incidence of tuberculosis greater than 1%, a tuberculosis test should be performed at baseline. All patients should undergo testing for reverse transcriptase and protease resistance mutations. HLA-B*5701 and chemokine receptor 5 (CCR5) tropism testing results must be confirmed prior to initiating therapy with either abacavir or maraviroc, respectively.

Chemistries should be drawn before beginning ART, but treatment may be started before results are available. NNRTIs (due to possible transmitted resistance) and abacavir (without HLA-B*5701 results) should not be used for rapid ART start. It should be noted that if ART is to be started immediately in the clinic, with no information yet available on viral load, CD4+ count, viral genotype, or HLA-B*5701 status, initial treatment is basically limited to a tenofovir-based regimen with an unboosted integrase strand transfer inhibitor (InSTI) or boosted darunavir. The presence of the M184I/V mutation, which confers resistance to lamivudine and emtricitabine, has been shown not to compromise the recommended regimens.

Case 1

Consider the case of a 48-year-old man presenting with newly diagnosed HIV infection. He is asymptomatic. His initial plasma HIV RNA level is 28,000...
Table 1. Antiretroviral Regimens for Initial Treatment for Most Patients

**Integrase strand transfer inhibitor-based regimens**
- Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)
- Dolutegravir (DTG) plus TAF/FTC
- DTG/lamivudine/abacavir
- DTG/lamivudine
- Raltegravir plus TAF/FTC (once daily)

**Protease inhibitor-based regimens**
- Cobicistat-boosted darunavir plus TAF/FTC

**Nonnucleoside inhibitor-based regimens**
- Rilpivirine/TAF/FTC
- Darunavir/lamivudine/tenofovir disoproxil fumarate (TDF)

TDF may be substituted for TAF if added cost or reimbursement restrictions exist.

Table 1 shows the ART regimens that are likely to be used most in initial treatment. Doravirine is a recently approved NNRTI with broad activity, including against reverse transcriptase inhibitor-resistant virus. Rilpivirine is still a good choice for many patients when the viral load is below 100,000 copies/mL. Table 2 lists recommended initial regimens if InSTIs are not available.

In monitoring patients after starting ART it is important to note that several antiretroviral drugs, such as dolutegravir, bictegravir, and ritonavir, are associated with an increase (eg, of 0.1–0.15 mg/dL) in serum creatinine level at a week after starting treatment in most patients. Like DTG, bictegravir inhibits the organic cation transporter 2 (OCT2) enzyme in the proximal renal tubule, resulting in a small increase in serum creatinine due to blockade of creatinine secretion; this has no effect on actual glomerular filtration rate.

**Case 2**
Consider the case of a 48-year-old man presenting with newly diagnosed HIV infection who is asymptomatic except for weight loss and fatigue and has a high initial viral load (760,000 copies/mL) and low CD4+ count (21 cells/µL). His other laboratory values are within normal limits and his HLA-B*5701 is positive. A regimen of DTG plus lamivudine, although not specifically recommended in either guidelines (yet), is an acceptable regimen in this case owing to the absence of baseline nRTI resistance mutations and recently presented 96-week data showing non-inferiority to standard InSTI-plus-2 nRTI regimens. A recent study showed no difference in attaining viral load levels below 50 copies/mL with bictegravir/TAF/FTC, DTG/abacavir/lamivudine, and DTG/TAF/FTC.

The difference between tenofovir disoproxil fumarate (TDF) and TAF should be noted. TDF is formulated as a 300 mg tablet and TAF as a 25 mg tablet. Higher plasma levels of TDF than TAF are needed to get sufficient amounts of tenofovir into cells. The higher plasma levels required for TDF are associated with increased adverse events. The use of TDF in regimens with boosted protease inhibitors (eg, boosted darunavir) appears to increase the adverse effects of TDF on bone and renal function.

**Case 3**
Consider the case of a 30-year-old woman with newly diagnosed HIV infection who is asymptomatic except for weight loss and fatigue and has a pretreatment HIV RNA level of 760,000 copies/mL. Regimens with DTG/lamivudine work well at viral load levels for individuals with between 100,000 and 500,000 copies/mL in the absence of resistance mutations, although there might be some hesitancy in using it in those patients with CD4+ counts below 200 cells/µL. Abacavir has been considered not to be a good choice if viral load is greater than 100,000 copies/mL; however, that rule of thumb is not relevant when abacavir is paired with DTG (rather than with a boosted PI or an NNRTI). In the study cited above among patients with viral load greater than 100,000 copies/mL, there was little difference in achieving viral load below 50 copies/mL with the bictegravir/TAF/FTC, DTG/abacavir/lamivudine, and DTG/TAF/FTC regimens.

Table 2. Recommended Initial Regimens if an Integrase Strand Transfer Inhibitor is Not Available.

- Darunavir/cobicistat/tenofovir alafenamide (TAF) (or tenofovir disoproxil fumarate [TDF])/emtricitabine
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine
- Efavirenz/TDF/emtricitabine
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine
- Raltegravir plus TAF (or TDF)/emtricitabine
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100,000 copies/mL and CD4+ cell count is >200/µL)

Adapted from Saag et al, *JAMA*, 2018.
infection. She is asymptomatic, has initial viral load of 128,000 copies/mL, and CD4+ count of 350 cells/µL. Her other laboratory findings are within normal limits and the HLA-B*5701 is negative. HIV genotyping shows reverse transcriptase mutations M184V and K103N. She has no notable prior medical history, no children, and does not plan to become pregnant. She is willing to start ART if her clinician thinks it advisable. What regimen should she be started on?

In this case the presence of M184V and K103N takes most NNRTI drugs off the table. The exception would be doravirine, which should maintain activity. The use of InSTI- and PI-based regimens remains the same. However, the presence of M184V removes the option of DTG plus lamivudine, which is contraindicated when this mutation is present. Moreover, TAF or TDF are preferentially used here over abacavir because the M184V partially weakens the activity of abacavir.

**Recommendations for Switching ART for Virologic Failure**

Recommendations for switching ART in cases of virologic failure have remained fairly constant for the past several years. Virologic failure should be confirmed and, if resistance is identified, there should be prompt switch to another active regimen. Recommended regimens after initial ART has failed are as follows:

- Dolutegravir or bictegravir plus 2 nRTIs (with at least 1 active as determined by genotype) after initial treatment failure with a regimen that contains an NNRTI
- A boosted PI plus 2 nRTIs (with at least 1 active nRTI) for initial treatment failure of an InSTI-containing regimen
- Dolutegravir plus at least 1 fully active other agent may be effective in the setting of raltegravir or elvitegravir resistance. Dolutegravir should be dosed twice daily in this setting. Of note, bictegravir should not be used here because it cannot be dosed twice daily owing to the fixed-dose formulation with TAF/emtricitabine

**Recommended Laboratory Monitoring**

The IAS–USA-recommended laboratory assessments and monitoring across the HIV continuum of care are shown in Table 3.

After starting ART, once the HIV RNA level is below 50 copies/mL, viral load should be monitored every 3 months until virus is suppressed for at least a year. Then, monitoring can be reduced to every 6 months if the patient maintains adherence. CD4+ cell count should be monitored every 6 months until counts are greater than 250/µL for at least 1 year with concomitant viral suppression. It is now recommended that CD4+ counts not be monitored thereafter unless virologic suppression is lost. CD4+ cell count monitoring is expensive and it is thought that little useful information is gained from continued routine monitoring in such a setting so long as viral suppression is maintained.

If a patient is found to have viral load above 50 copies/mL, testing should be repeated within 4 weeks and the patient reassessed for adherence and medication tolerability. Measurement of viral load at 4 to 6 weeks after starting a new ART regimen is recommended. The test should be repeated within 4 weeks if HIV RNA level remains above the limit of quantification 24 weeks after starting new treatment or if rebound above 50 copies/mL occurs. Tropism testing should be performed at the time of virologic failure of a CCR5 inhibitor.

Age- and risk-appropriate screening for STIs at various anatomical sites should continue, with testing for anal or cervical dysplasia, sexually transmitted infections (especially syphilis), and monitoring for general health and

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**Table 3. International Antiviral Society–USA Recommendations for Laboratory Assessments and Monitoring Across the HIV Continuum of Care.**

<table>
<thead>
<tr>
<th>Test</th>
<th>At HIV Diagnosis</th>
<th>During ART</th>
<th>At Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA level</td>
<td>✓</td>
<td>Within the first 6 weeks of starting ART or a new ART regimen, then every 3 months until &lt;50 copies/mL for 1 year, then every 6 months</td>
<td>✓</td>
</tr>
<tr>
<td>CD4+ cell count</td>
<td>✓</td>
<td>Every 6 months until &gt;250/µL for 1 year then stop as long as virus is suppressed</td>
<td>✓</td>
</tr>
<tr>
<td>HIV RT-pro genotype</td>
<td></td>
<td>If failing ART regimen included an InSTI</td>
<td></td>
</tr>
<tr>
<td>HIV integrase genotype</td>
<td></td>
<td>Each time before the start of ART that includes maraviroc</td>
<td></td>
</tr>
<tr>
<td>Viral tropism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>✓ (before initiating abacavir; just once)</td>
<td>✓ (if considering abacavir and not determined previously)</td>
<td></td>
</tr>
<tr>
<td>Safety testing</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Coinfection (STIs, tuberculosis, hepatitis, Pap test)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Health maintenance</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Adapted from Saag et al, JAMA, 2018

Abbreviations: ART indicates antiretroviral therapy; InSTI, integrase strand transfer inhibitor; STI, sexually transmitted infection.
medication toxicity continued on a regular basis.

**Regimens in Individuals Who Are Pregnant or Considering Pregnancy**

**Case 4**

Consider the case of a 30-year-old woman presenting with newly diagnosed asymptomatic HIV infection. She is 2.5 months pregnant, with her first pregnancy. Her initial viral load is 28,000 copies/mL and CD4+ cell count is 650/µL. Other laboratory values are within normal limits; she is HLA-B*5701-negative. Genotyping shows wild-type virus. She had no prior notable medical history and is willing to start ART if her clinician thinks it advisable. On what ART regimen should she be started?

In patients who are pregnant or anticipate becoming pregnant, additional considerations related to potential teratogenicity, placental transfer of drugs, and medication tolerability during pregnancy come into play. Most of the drugs recommended for use as initial regimens, such as rilpivirine, efavirenz, ritonavir boosted-atazanavir or -darunavir, or raltegravir are all acceptable anchor drugs for ARV regimens in pregnant women.

Abacavir, TDF, emtricitabine and lamivudine are all acceptable nRTI drugs for use in pregnancy. However, insufficient data exist regarding the use of TAF, bictegravir, and cobicistat, and these drugs should be avoided until more data emerge regarding their efficacy and safety in the setting of pregnancy.

The use of DTG is controversial. In southern Africa, where dolutegravir was widely adopted as a component of initial therapy for all patients living with HIV, a signal of approximately 4-fold increase in neural tube defects (NTDs) occurring in infants born to mothers taking DTG-based regimens during the first trimester (of note, effect on neural tube development was noted when DTG was initiated after 8 weeks gestation owing to the timing of neural tube closure approximately week 6 of gestation). Follow-up data obtained over the subsequent 2 years following the initial reports of NTD have shown a reduction in incidence toward those reported among mothers not taking DTG. Further data are needed, but it seems likely that the initial signal of increased incidence of NTD is dissipating as higher numbers of mothers have been followed. Of note, the mechanism of NTD appears related to relatively low maternal folate levels. Therefore, use of folate supplementation is suggested for all women taking DTG who are contemplating pregnancy or who are in their first trimester of pregnancy.

**Should Regimens be Changed When Low Level Detectable Virus Is Present?**

**Case 5**

Consider the case of a 55-year-old man diagnosed 18 years ago with HIV infection, with initial viral load of 936,000 copies/mL and CD4+ count of 70 cells/µL. His current viral load is 85 copies/mL, after a prior level of 62 copies/mL, and CD4+ count is 525 cells/µL. His initial treatment was nevirapine/stavudine/lamivudine. He has subsequently received ritonavir-boosted lopinavir plus TDF/emtricitabine, efavirenz plus TDF/emtricitabine, and is now on DTG plus darunavir/cobicistat/lamivudine. No historical resistance tests are available. Given the detectable viral load, should the ART regimen be changed?

In such a situation, there is little rationale for altering the patient’s ART regimen. There is no clear indication that any regimen would do better or even that adding another drug (eg, TDF or TAF) would result in a change in viral load. These blips in viral load are related to residual viral reservoir cells—or chronically latently infected cells—that get stimulated occasionally to ‘spit out’ some virus. Viral load is directly proportional to the number of cells in the body that are producing virus. In patients who have very high viral loads prior to treatment, a large number of reservoir cells are established, with viral blips occurring over time even in the context successful suppression of all de novo infection in vivo. It is estimated that these chronically latently infected cells have a half life on the order of 80 months. No change in ART is going to affect this phenomenon until curative therapy is developed. However, an increase in viral load to greater than 200 copies/mL, for example, is cause for concern regarding potential virologic failure and should be investigated.

**Sexual Transmission Risk for Patients with Undetectable HIV RNA**

A patient with continuously undetectable viral load has zero, or virtually zero, likelihood of sexually transmitting infection to an uninfected partner. As shown in Figure 1, a recent study showed no linked transmissions of infection from infected to HIV-seronegative partners over the course of approximately 77,000 sex acts over nearly 1600 couple-years of follow up.

**Table 4. HIV Transmission According to Sexual Behavior Reported By the HIV-Seronegative Partners Over 2700 Couple Years of Follow Up.**

<table>
<thead>
<tr>
<th>Linked transmission</th>
<th>Upper 95% CI</th>
<th>CYFU</th>
<th>CLS acts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sex</td>
<td>0.23</td>
<td>1596</td>
<td>76991</td>
</tr>
<tr>
<td>Anal sex</td>
<td>0.24</td>
<td>1546</td>
<td>70743</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>0.27</td>
<td>1345</td>
<td>52572</td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>0.57</td>
<td>652</td>
<td>20770</td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>0.43</td>
<td>867</td>
<td>23153</td>
</tr>
<tr>
<td>Any sex with a STI</td>
<td>2.74</td>
<td>135</td>
<td>6301</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CYFU, couple years of follow up; CLS, condomless sex acts; STI, sexually transmitted disease.
References


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