CROI 2014: Viral Hepatitis and Complications of HIV Disease and Antiretroviral Therapy

Anne F. Luetkemeyer, MD; Diane V. Havlir, MD; and Judith S. Currier, MD

The remarkable advances in interferon-sparing, all-oral hepatitis C virus (HCV) treatment were a highlight of the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). The backbone of the nucleotide inhibitor sofosbuvir and the nonstructural protein 5A (NS5A) inhibitor ledipasvir with an additional third agent (HCV protease inhibitor or HCV nonnucleoside reverse transcriptase inhibitor) led to a sustained virologic response (SVR) rate 12 weeks after cessation of treatment of 95% to 100% after only 6 weeks of treatment. These results demonstrate the potential of combination direct-acting antiviral (DAA) therapy for abbreviated, well-tolerated, and highly effective HCV treatment. Two triple-drug regimens that comprised 12 weeks of an NS5A inhibitor, an HCV protease inhibitor, and a nonnucleoside inhibitor also resulted in SVRs of more than 90% in patients with HCV genotype 1. HIV coinfection does not appear to negatively impact response to DAA-based HCV therapy, as evidenced by similar response rates in HIV/HCV-coinfected patients compared with HCV-monoinfected patients receiving interferon-sparing or -containing regimens. There was continued emphasis at CROI 2014 on non-AIDS complications of HIV infection, specifically cardiovascular disease, renal insufficiency, and bone and endocrine disorders that persist among patients with treated HIV disease and contribute to morbidity and mortality. Finally, new data on novel drugs and combinations for treatment of tuberculosis (TB), patient outcomes using new rapid TB diagnostics, and a short-course TB prevention strategy were presented.

Keywords: CROI 2014, HIV, hepatitis C virus, HCV, direct-acting antivirals, antiretroviral therapy, coinfection, comorbidities, cardiovascular disease, bone, aging, Kaposi sarcoma, tuberculosis

Overview of Hepatitis C Virus Direct-Acting Antiviral Drugs: Present and Future

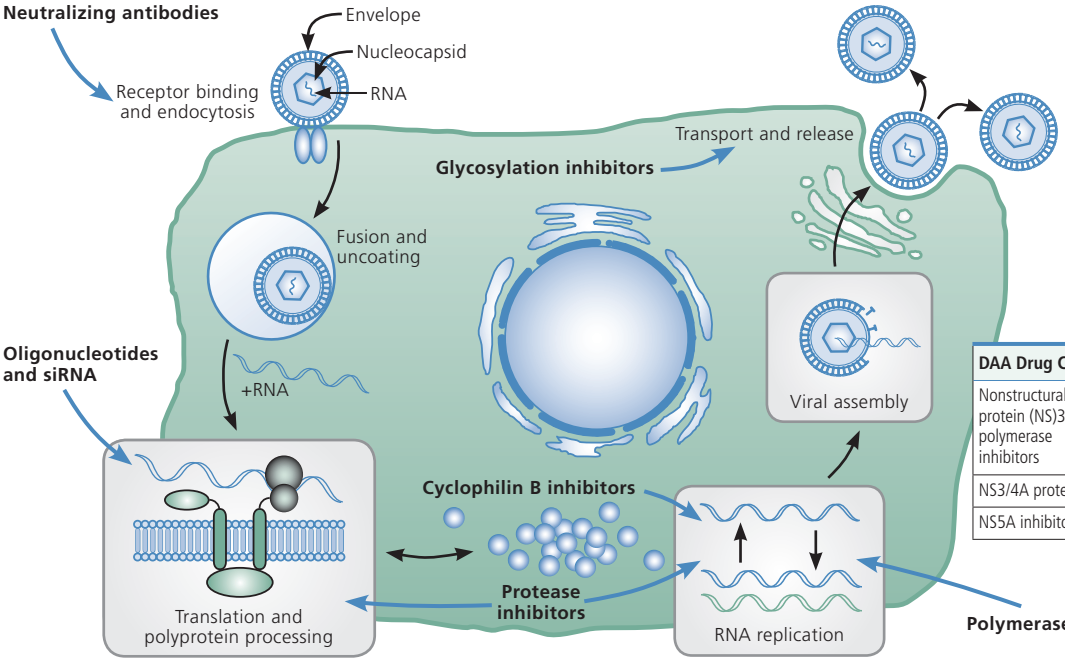
Dramatic advances in the treatment of hepatitis C virus (HCV) with short, well-tolerated, highly effective oral regimens were a highlight of the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014. A summary of the current classes of direct-acting antiviral (DAA) drugs and their sites of action during HCV replication are presented in Figure 1. Pawlotsky gave a comprehensive overview of DAAs and the anticipated pathways for use of all-oral DAA therapy in HCV infection (Abstract 60), highlighting 2 key summary points.

First, HIV/HCV-coinfected patients have demonstrated an excellent and generally equivalent response to DAA regimens. Thus, coinfected patients should no longer be expected to have a suboptimal response on the basis of HIV coinfection, as was the case in the pre-DAA, interferon-based treatment era. It will still be important to evaluate HCV regimens in coinfected patients to ensure that there are no adverse interactions between antiretroviral and DAA drugs, and to confirm that HIV is not negatively impacting response to novel HCV combinations. Second, Pawlotsky outlined 3 main pathways that have emerged in HCV DAA drug development: (1) a nucleotide inhibitor backbone (eg, sofosbuvir) in combination with 1 or 2 additional DAA drugs; (2) nucleoside-sparing triple therapy, typically a combination of an HCV protease inhibitor (PI), an HCV nonstructural protein 5A (NS5A) inhibitor, and a nonnucleoside inhibitor; and (3) dual therapy with a second-generation HCV PI and an NS5A inhibitor (eg, MK-5172 and MK-8742 or ACH-2684 and ACH-3102). Most of these strategies are expected to be effective without the need for ribavirin.

Nucleos(t)ide Inhibitor–Based Regimens

The National Institutes of Health SYNERGY study evaluated a fixed-dose, once-daily combination of the nucleotide analogue NS5B polymerase inhibitor sofosbuvir and the investigational NS5A inhibitor ledipasvir in a US urban population with genotype 1 HCV infection (Abstract 27LB). Subjects were characterized by a high proportion of risk factors traditionally predictive of poor response to HCV treatment; 88% of subjects were African American, 70% had HCV genotype 1a, 70% had HCV RNA levels above 800,000 IU/mL, and 80% had less favorable IL28b, non-CC genotypes. In arm A of the study, sofosbuvir and ledipasvir given for 12 weeks led to a sustained virologic response (SVR) rate 12 weeks after cessation of treatment (SVR12) of 100% (20 of 20). Arm A permitted subjects with cirrhosis (15% with Knodell fibrosis scores of 4), and arms B and C of the study excluded subjects with

Dr Luetkemeyer is Associate Professor of Medicine at University of California San Francisco (UCSF), San Francisco General Hospital. Dr Havlir is Professor of Medicine at UCSF and Chief of the HIV/AIDS Division at San Francisco General Hospital. Dr Currier is Chief of the Division of Infectious Diseases at University of California Los Angeles. Send correspondence to Anne F. Luetkemeyer, MD, 995 Potrero Ave, Box 0874, San Francisco, CA 94110. Received on March 26, 2014; accepted on April 16, 2014.



DAA Drug Class		Examples
Nonstructural protein (NS)3b polymerase inhibitors	Nucleos(t)ide inhibitors	Sofosbuvir
	Nonnucleoside inhibitors	ABT-333[a], GS-9669[a]
NS3/4A protease inhibitors		Simeprevir, MK-5172[a]
NS5A inhibitors		Daclatasvir[a], ledipasvir[a]

Figure 1. Hepatitis C virus (HCV) direct-acting antiviral (DAA) drug classes and site of action during HCV replication. Adapted from Asselah and Marcellin.[30] [a]Investigational drug.

cirrhosis. In arm B, sofosbuvir and ledipasvir given with the nonnucleoside inhibitor GS-9669 for 6 weeks resulted in an SVR12 of 95% (19 of 20) with 1 subject relapsing at week 4 after therapy. In arm C, sofosbuvir and ledipasvir given with the HCV PI GS-9451 for 6 weeks resulted in an SVR12 of 100% (20 of 20). Treatment was generally well tolerated with the most common adverse effects being headache, fatigue, and diarrhea. There were no discontinuations or serious adverse events related to study medications. The 6-week regimens of sofosbuvir and ledipasvir used with either an HCV PI or a nonnucleoside inhibitor are currently being evaluated in subjects with cirrhosis, and a 4-week regimen is also being evaluated.

SYNERGY represents a remarkable step forward in HCV treatment, with near universal cure rates in a relatively hard-to-treat population using 6 weeks of all-oral, well-tolerated therapy that did not include interferon or ribavirin. These results raise the possibility of shortening HCV therapy even further (ie, 4 weeks), potentially with the addition of a fourth agent (an HCV PI or a nonnucleoside inhibitor). Of note, sofosbuvir has been approved for use by the US by Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Ledipasvir in combination with sofosbuvir is under FDA review.

Additional results were presented from the PHOTON-1 study (Abstract 26), evaluating the use of sofosbuvir with weight-based ribavirin in HIV/HCV-coinfected patients. Raltegravir, rilpivirine, ritonavir-boosted (/r) darunavir, atazanavir/r, efavirenz, and emtricitabine plus tenofovir were permitted as antiretroviral therapy. For HCV treatment–naive patients, SVR12 rates were 76% (87 of 114) in patients with HCV genotype 1 infection who received 24 weeks of treatment, 88% (23 of 26) in patients with HCV genotype 2 infection who received 12 weeks of treatment, and 67% (28 of 42) in patients with HCV genotype 3 who received 12 weeks of treatment. Among these treatment-naive subjects, 25 with HCV genotype 1 and 12 with HCV genotype 3 had confirmed virologic relapse; no patients with HCV genotype 2 experienced relapse. No sofosbuvir resistance was documented in the relapsers.

For treatment-experienced patients, the SVR12 rate for those with HCV genotype 2 was 92% (22 of 24) and was 94% (16 of 17) for those with HCV genotype 3, each with 24 weeks of therapy. It is notable that the SVR rate was considerably higher in treatment-experienced patients with HCV genotype 3 than was seen in the VALENCE study, which also investigated sofosbuvir and ribavirin for 24 weeks in HCV genotype 3–monoinfected patients.[1] In the VALENCE study, SVR12 rates were 87% (87 of 100) in treatment-experienced patients without cirrhosis and 60% (27 of 45) in treatment-experienced patients with cirrhosis. Twenty-four percent (10 of 41) of treatment-experienced subjects with HCV genotype 2 or 3 in the PHOTON-1 study had cirrhosis; however, data on SVR12 rates in patients with HCV genotype 3 was not broken down into those who had cirrhosis and those who did not have cirrhosis. In terms of tolerability, most subjects experienced some adverse effects, most commonly fatigue, insomnia, headache, nausea, and diarrhea. Grade 3 or 4 adverse events occurred in 10% to 12% of participants, with treatment-limiting adverse effects occurring in 3% to 4%.

In general, response rates in the PHOTON-1 study are very similar to

those seen in HIV-uninfected patients, providing additional evidence that HIV is no longer a risk factor for poor response to HCV treatment in the current DAA treatment era. Sofosbuvir plus ribavirin is a currently available treatment option that produces excellent SVR rates with 12 weeks of therapy in patients with HCV genotype 2 infection. Treatment should be extended to 24 weeks in patients with HCV genotypes 1 or 3. The PHOTON-1 study did not evaluate sofosbuvir and ribavirin in treatment-experienced patients with HCV genotype 1 infection.

Nucleoside-Sparing Regimens: Triple Therapy

The AI443-014 study (Abstract 25) evaluated HCV-monoinfected treatment-naive patients with HCV genotype 1 (9% with cirrhosis) who were treated with 12 weeks of an investigational, twice-daily regimen of the NS5A inhibitor daclatasvir, the HCV PI asunaprevir, and the nonnucleoside polymerase inhibitor BMS-791325 (dosed at 75 mg or 150 mg daily). SVR12 rates were 92.2% with 75 mg of BMS-791325 and 91.7% with 150 mg of BMS-791325. Response rates were generally similar between subjects with or without cirrhosis, with a marginally lower response rate in subjects with HCV genotype 1a (91%) than in those with genotype 1b (94% to 100%), and in those with the less favorable IL28B non-CC genotypes (89% to 91%) than in those with the favorable IL28b CC genotype (96%). Of note, all on-treatment virologic breakthrough (5 of 166) and post-treatment relapses (6 of 166) occurred in participants with HCV genotype 1a infection. Of the 11 failures, 6 had HCV virus resistant to all 3 HCV DAAs and 5 had virus resistant to daclatasvir and asunaprevir. Baseline polymorphisms associated with resistance were not associated with treatment failure in patients with HCV genotype 1a.

Although treatment failure was uncommon, association of failure with 2- or 3-class resistance has important implications for subsequent HCV retreatment, which at least in the short term would need to exclude NS5A, HCV PI, and nonnucleoside inhibitor use due to anticipated cross-resistance within these classes with most drugs currently in development. The most common adverse effects were headache, diarrhea, fatigue, and nausea, with no treatment-related serious or grade 3 or 4 adverse events. This triple-therapy, all-oral regimen is promising for genotype 1 HCV infection, with the caveat that patients with genotype 1a may be more vulnerable to treatment failure with emergence of HCV resistance. More data are needed to understand the duration of HCV resistance mutations after treatment failure and the implications for cross-resistance with newer DAAs in development.

Another promising triple-drug regimen in development is the investigational combination of the HCV PI ABT 450/r, coformulated in a single pill with the NS5A inhibitor ABT-267, and the nonnucleoside polymerase inhibitor ABT-333, given with or without ribavirin, evaluated in the PEARL-III study. HCV-monoinfected, treatment-naive participants who did not have cirrhosis were randomized to receive triple therapy, with or without ribavirin, for 12 weeks (Abstract 29LB). SVR12 rates were 99.5% with ribavirin and 99% without ribavirin, suggesting that ribavirin is not a necessary component for patients with HCV genotype 1b infection. Similar results were obtained in the PEARL-II study, with HCV genotype 1b–infected, treatment-experienced patients attaining SVR12 rates of 97% with ribavirin and 100% without ribavirin.[2] In the PEARL-IV study, this triple-drug regimen led to SVR12 rates of 97% with ribavirin and 90% without ribavirin in treatment-naive patients with HCV genotype 1, indicating that ribavirin may be more important for curative therapy of subjects with genotype 1a.[2] In the current PEARL-III study, there were no virologic failures in the arm that did not contain ribavirin and 1 virologic rebound posttreatment in the ribavirin-containing arm, with emergence of an NS5A resistance mutation (Y93H). The most common adverse effects were headache and fatigue; anemia occurred in the ribavirin-containing arm only. There were no treatment-related study discontinuations.

The same triple-drug regimen plus ribavirin was evaluated in an open-label study, M14-103, of treatment-naive or -experienced HCV genotype 1–monoinfected patients who did not have cirrhosis and were on stable opiate replacement therapy with buprenorphine (19 of 38) or methadone (19 of 38) (Abstract 662LB). The SVR12 rate was 97.4% (37 of 38), which is comparable to SVR rates attained in other studies of this triple-drug regimen in treatment-naive and -experienced patients with HCV genotype 1 infection. One participant discontinued early because of stroke and a high-grade sarcoma diagnosis that were judged unrelated to study treatment. There were no virologic failures and no patients required changes in dosage of methadone or buprenorphine. This study provides promising pilot data to support use of this triple-drug regimen in patients on opiate substitution therapy, which is common in the HCV-infected population.

The nucleoside-sparing dual therapy of daclatasvir and the HCV PI simeprevir, given with or with ribavirin, was evaluated in the LEAGUE-1 study (Abstract 28LB). HCV genotype 1–monoinfected patients who were either treatment naive or had prior null responses were randomized to receive daclatasvir and simeprevir with or without ribavirin. Patients with HCV genotype 1a received 24 weeks of treatment and patients with genotype 1b were randomized to 12 weeks or 24 weeks of treatment. Importantly, daclatasvir was dosed at 30 mg, a dose reduction based on healthy volunteer data indicating that simeprevir coadministration led to a 2-fold decrease in daclatasvir concentrations. On-study daclatasvir concentrations were lower than anticipated and may have affected the efficacy of this regimen. Treatment-naive patients with HCV genotype 1a had an SVR12 rate of 67% (8 of 12), with 33% (4 of 12) experiencing virologic breakthrough on treatment. Resistance data were not presented. The first 5 HCV genotype 1a–infected patients with prior

null response enrolled in the study all experienced virologic breakthrough and were offered peginterferon alfa and ribavirin in addition to daclatasvir and simeprevir. Treatment-naive participants with HCV genotype 1b infection fared better, attaining SVR12 rates of 81% with 12 weeks and 89% with 24 weeks of treatment with daclatasvir and simeprevir without ribavirin; SVR12 rates were 75% and 74%, respectively, with the addition of ribavirin. Thus, in treatment-naive patients with HCV genotype 1b, ribavirin did not improve SVR, and extending therapy to 24 weeks only marginally improved response. However, in patients with prior null response (never achieved a ≥ 2 $\log_{10}$ IU/mL drop in HCV RNA level after ≥ 12 weeks of prior treatment) ribavirin did impact cure, with ribavirin-sparing therapy yielding SVR12 rates of 83% with 12 weeks of treatment and 50% with 24 weeks of treatment compared with ribavirin-containing therapy that yielded SVR12 rates of 100% and 89%, respectively. Overall, these data indicate that the likely suboptimal dosing of 30 mg of daclatasvir coadministered with simeprevir is generally not sufficiently potent for patients with HCV genotype 1a but works well for patients with HCV genotype 1b. However, HCV genotype 1b–infected patients with prior null response may benefit from the addition of ribavirin. There did not appear to be a benefit to extending treatment to 24 weeks in patients with HCV genotype 1b. It is not known if increasing daclatasvir dose when given with simeprevir would have improved the regimen potency, particularly in subjects with HCV genotype 1a.

Second-Generation Combination Strategies

Data were presented from part B of the C-WORTHY study, evaluating the second-generation investigational HCV PI MK-5172, which has shown a higher barrier to resistance than earlier HCV PIs, coadministered with the investigational NS5A inhibitor MK-8742 in a once-daily oral regimen (Abstract 654LB). Part A of this trial demonstrated SVR24 rates of 89% to 100% with 12 weeks of treatment with MK-5172 and MK-8742 given with or without ribavirin in HCV-monoinfected, treatment-naive patients with HCV genotype 1a or 1b who did not have cirrhosis.[3] Part B evaluated 12 weeks of MK-5172 and MK-8742 given with or without ribavirin to 59 HIV/HCV-coinfected patients. Response rates were compared with those of 65 HCV-monoinfected patients enrolled in part A of the study. Both groups had HCV genotype 1, were treatment-naive, and did not have cirrhosis. Permitted antiretroviral therapy was raltegravir and 2 nucleos(t)ide reverse transcriptase inhibitors (nRTIs).

At the end of 12 weeks of treatment with MK-572 and MK-8742 plus ribavirin, virologic response (HCV RNA level < 25 IU/mL) by intent-to-treat analysis was attained in 100% (29 of 29) of HIV/HCV-coinfected participants and in 94% (49 of 52) of HCV-monoinfected participants. Treatment with MK-5172 and MK-8742 alone produced virologic response in 90% (26 of 29) of HIV/HCV-coinfected participants and in 100% (13 of 13) of HCV-monoinfected participants. Two HIV/HCV-coinfected patients experienced HCV virologic breakthrough in the ribavirin-sparing arm and both patients had low MK-5172 and MK-8742 levels on treatment. SVR12 data are not yet available. There did not appear to be a difference in response between HIV-infected and -uninfected subjects. Virologic breakthrough only occurred in 2 HIV-infected subjects and the numbers are too small to conclude whether HIV infection increases the risk of virologic breakthrough. Healthy volunteer pharmacokinetic data found no meaningful drug interactions between MK-5172 or MK-8742 coadministered with raltegravir or tenofovir (Abstracts 498 and 500). Thus, it seems unlikely that raltegravir or NRTIs led to suboptimal MK-5172 and MK-8742 concentrations. Treatment was well tolerated and the most common adverse effects were fatigue, headache, nausea, and diarrhea; no subjects discontinued therapy due to treatment-associated adverse events.

Peginterferon Alfa–Containing Regimens

Given the remarkable efficacy of all-oral, peginterferon alfa–sparing regimens, there is a limited role for the current use of peginterferon alfa because of the duration required and the considerable associated toxicity; it is anticipated that there will be no role for peginterferon alfa–containing regimens in the future. Because lower SVR rates (68% to 72%) were attained with 24 weeks of treatment with sofosbuvir and weight-based ribavirin (PHOTON-1 [Abstract 26] and SPARE[4] trials) than with sofosbuvir plus peginterferon alfa and ribavirin, 12 weeks of peginterferon alfa and ribavirin with sofosbuvir may be preferable for eligible patients with HCV genotype 1 infection until more DAAs become available, particularly for those who are treatment experienced. Although peginterferon alfa–based regimens will be of limited use as availability of interferon-sparing regimens increases, data from interferon-containing regimens can still provide insight into efficacy, tolerability, and comparative performance in HIV-infected and -uninfected individuals.

The C212 study evaluated the HCV PI simeprevir, which is currently approved for use by the FDA (Abstract 24). One hundred six HIV/HCV-coinfected participants with HCV genotype 1 infection received 12 weeks of once-daily simeprevir. Treatment-naive patients and those with prior relapse received 24 weeks to 48 weeks of accompanying peginterferon alfa and ribavirin, depending on treatment response. Treatment-experienced patients (partial and null response) and those with cirrhosis received 48 weeks of peginterferon alfa and ribavirin. Because simeprevir is metabolized by cytochrome P450 3A4, antiretroviral therapy was restricted to raltegravir, rilpivirine, maraviroc, enfuvirtide, and NRTIs. SVR12 rate was 74% overall, 79% in treatment-naive patients, 87% in those with prior relapse, 70% in those with prior partial response, and 57% in those with prior null response. These SVR rates are comparable to those of HCV-monoinfected patients (80%-81%

in treatment-naive patients, 79%-88% in those with prior relapse, 65%-86% in those with prior partial response, and 58% in those with null response[5-7]). As seen with previous peginterferon alfa and ribavirin regimens, IL28B status affected response. The favorable IL28b CC allele was associated with a 96% SVR12 rate, whereas SVR12 rates with the less favorable alleles were 68% (CT) and 61% (TT). There was a trend toward decreased SVR12 rates with more advanced fibrosis (64% with Metavir score F3-F4 vs 80% with F0-F2) and with HCV genotype 1a compared with genotype 1b (71% vs 89%, respectively). Of note, baseline presence of the HCV protease Q80K polymorphism was not associated with a substantially decreased SVR12 rate (67% in those with Q80K vs 72% in those without Q80K), despite a previous association of Q80K with a 26% decrease in SVR12 rates in HCV monoinfection studies of simeprevir with peginterferon alfa and ribavirin in patients with HCV genotype 1.[8]

The safety profile was similar to other peginterferon alfa–based regimens, with 10% of patients experiencing serious adverse events. Simeprevir is associated with rash, pruritus, photosensitivity which can be severe, and elevated bilirubin levels. Overall, the C212 study demonstrates that HIV/HCV-coinfected patients can attain cure rates equivalent to their HCV-monoinfected counterparts, which has been shown with other HCV PIs when given with peginterferon alfa and ribavirin. Although simeprevir use with peginterferon alfa and ribavirin will be limited by interferon-related toxicity and lengthy treatment duration, simeprevir is under investigation as part of all-oral, interferon-sparing regimens, including simeprevir with sofosbuvir (COSMOS [Combination of Simeprevir and Sofosbuvir in HCV Genotype 1 Infected Patients] study[9]) and simeprevir with daclatasvir (LEAGUE-1 study).

The STARTVerso 4 study evaluated the investigational HCV PI faldaprevir, also given in combination with peginterferon alfa and ribavirin, in HIV/HCV-coinfected patients with HCV genotype 1 (Abstract 23). Three hundred nine subjects received 12 weeks to 24 weeks of faldaprevir in conjunction with 24 weeks to 48 weeks of peginterferon alfa and ribavirin, depending on treatment response; 17% had fibrosis (F4). Permitted antiretroviral therapy was raltegravir, maraviroc, efavirenz, darunavir/r, atazanavir/r, and NRTIs. Because of anticipated drug interactions, faldaprevir was dosed at 240 mg with efavirenz, 120 mg with the HIV PIs, and patients were randomized to 120 mg or 240 mg with raltegravir and maraviroc. The overall SVR12 rate was 72%, with 80% of patients qualifying for shortened therapy (24 weeks) and 89% of these attaining SVR. Interestingly, the SVR12 rate was higher in those with prior relapse than in those who were treatment naive (83% vs 69%, respectively; $P = .02$). HCV genotype 1a, cirrhosis, or the presence of the Q80K polymorphism did not negatively impact SVR12 rates. The safety profile was similar to other interferon-containing regimens, with adverse events triggering discontinuation in 7% of patients. As with simeprevir plus peginterferon alfa and ribavirin, SVR12 rates with faldaprevir plus peginterferon alfa and ribavirin were nearly identical to what has been seen in the HCV-monoinfected population,[10,11] reiterating that HIV does not appear to negatively impact response with DAA-based therapy.

Pharmacokinetic data from the STARTVerso 4 study found that faldaprevir reduced mean darunavir trough levels, reduced raltegravir concentrations only when faldaprevir was dosed at 240 mg daily, and had no notable effect on efavirenz or atazanavir; the investigators indicated that the impact on antiretroviral therapy is not clinically significant (Abstract 497). Interestingly, raltegravir drug concentrations were increased 2.7-fold by faldaprevir 240 mg daily in a study of healthy volunteers, suggesting that pharmacokinetic interactions in HIV-uninfected volunteers on single-drug HCV or HIV therapy cannot always be generalized to HIV-infected patients on combination antiretroviral therapy (Abstract 501).

Complications of HCV Infection

The systemic impact of HCV beyond strictly liver-related complications is increasingly recognized. In an observational cohort of US veterans, patients with detectable HCV RNA levels and unfavorable lipid profiles had a 22% to 64% increased risk of myocardial infarction (MI). Individuals with undetectable HCV RNA levels had a less pronounced increase in coronary artery disease risk at each unfavorable lipid stratum, suggesting that chronic HCV infection contributes to coronary disease risk (Abstract 685). In another US veteran cohort analysis, HIV/HCV coinfection was associated with higher risks of stroke, congestive heart failure, and venous thromboembolism than were seen with HIV or HCV monoinfection, after adjusting for traditional cardiovascular risk factors (Abstract 688).

HCV infection was independently associated with low bone mineral density (BMD) at hip, spine, and femoral neck, which may be mediated through elevated levels of regulatory cytokines receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) suppressing bone turnover. The investigators suggested that this is a different pathophysiologic mechanism than HIV-associated low BMD, which may be mediated in part by high bone turnover and tenofovir use. HCV-associated low BMD was not correlated with hepatic fibrosis, as assessed by aspartate aminotransferase (AST)-to-platelet ratio index (APRI) (Abstract 783). In terms of liver-related mortality, a EuroSIDA analysis demonstrated that liver-related deaths accounted for 27% of all deaths in HIV/HCV-coinfected patients, which was similar to the AIDS-related death rate (Abstract 652). Predictors of liver-related mortality included fibrosis of F2 or more (adjusted subhazard ratio [sHR] 28.3; $P < .024$), low CD4+ cell count, and hepatitis B virus (HBV) coinfection (sHR 6.57; $P = .013$). HCV viremia and duration of infection were also statistically significantly associated with increased risk of non–liver-related death (sHR 1.54 and 1.34 per 5 years, respectively). In

a French cohort, HIV/HCV-coinfected individuals had a higher hazard ratio (HR) of all-cause mortality of 1.79 ($P < .001$) than HIV-monoinfected patients (Abstract 690). Non–liver-related mortality (HR 1.4; $P < .001$) and nonliver, non–AIDS-related mortality (HR 1.47; $P < .001$) were also statistically significantly increased in HIV/HCV coinfection. Collectively, these data are an important reminder of the systemic impact that chronic HCV infection can have on hepatic, cardiovascular, and skeletal health, and of the impact of HCV on overall mortality, including non–liver-related death. The emerging availability of shorter, better-tolerated, and highly effective HCV curative therapy has enormous potential to impact the morbidity and mortality associated with HCV.

Hepatitis B Virus and Hepatitis Delta Virus

Currently, active HBV drugs are nucleos(t)ides that target the HBV polymerase or the immune modulator interferon. There is a marked need for drugs with other HBV targets, to improve control of HBV viremia and perhaps ultimately eradicate HBV, which is not possible with current therapies.

Kottililll gave an excellent talk reviewing a number of HBV drugs in development with novel targets of action, including HBV entry inhibitors (Myrcludex-B), covalently closed circular DNA inhibitors or silencers (zinc finger motifs), HBV capsid inhibitors (BAY 41-4109), hepatitis B surface antigen secretion inhibitors (HBF-0259), and host-directed therapies such as Toll-like receptor 7 agonists (GS-9620), programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) antibodies, and therapeutic vaccination (Abstract 58). These therapies are all quite early in development but hold promise for more robust HBV treatment in the future.

Isolated HBV core antigen positivity presents a challenge to the treating clinician as it may represent resolved HBV infection with undetectable hepatitis B surface antibody level, the window period in acute HBV infection, a false positive test result, or clinically significant occult HBV infection. One abstract found an association between isolated HBV core antibody positivity and advanced fibrosis (assessed by FIB-4 or APRI) in HIV/HCV-coinfected patients (Abstract 695). This association was not seen in HIV/HCV-coinfected patients from the WIHS (Women's Interagency HIV Study) cohort, where fibrosis was assessed by enhanced liver fibrosis (ELF) markers (Abstract 696). Further data are needed to identify which HIV-infected patients with isolated HBV core antibody positivity are truly at risk for progression of fibrosis.

Hepatitis delta virus (HDV) superinfection of HBV can lead to severe liver fibrosis, and there are limitations to treatment with peginterferon alfa.[12,13] In a cohort of 19 HIV/HBV/HDV-coinfected patients who received a median of 58 months of tenofovir as part of their HIV treatment, 100% attained undetectable HBV DNA levels and 53% (10 of 19) had HDV RNA levels below 10 copies/mL (Abstract 700). Substantial liver fibrosis regression (defined as a 30% reduction in hepatic stiffness measured by elastography) occurred in 60% (6 of 10) of patients with undetectable HDV RNA levels and did not occur in 9 patients with persistent HDV viremia. These data suggest that tenofovir may play an important role in the control of HDV infection, although treatment was not sufficient to suppress HDV in all patients during the 3- to 7-year study period.

Hepatitis E Virus

Hepatitis E virus (HEV) is found worldwide and is typically an acute, self-limiting viral hepatitis. However, HEV infection is increasingly recognized as a cause of chronic viral disease, particularly in immunosuppressed individuals, and can lead to liver fibrosis and decompensation. Sherman comprehensively reviewed HEV (Abstract 57). Transmission of HEV genotypes 1, 2, and 4 is associated with poor sanitation and contaminated water. However, HEV genotype 3 is transmitted via contact with pigs and pork products, deer, shellfish, and through parenteral exposure. Diagnosis of HEV can be challenging—there is no FDA approved test for HEV, and there is a short duration of immunoglobulin M (IgM) positivity and HEV RNA viremia during acute illness, which limits the window for diagnosis. HEV should be in the differential for acute hepatitis in HIV infection—it was detected in 3% to 4% of acute hepatitis episodes in a US study of HIV-infected individuals[14] and in 2% to 9% in European studies[15-18]—and may lead to hepatic decompensation in the setting of acute or chronic disease. Diagnoses of HEV infection were made through detection of HEV IgM, IgG, and RNA.

Chronic HEV infection is uncommon but can occur in patients with HIV coinfection, those who have received a solid organ transplant, or those with hematologic malignancy, and may be an underrecognized cause of transaminitis and hepatic decompensation. A study in northern Spain found an HEV seroprevalence of 9.8% in HIV-infected patients, with none developing chronic HEV infection (Abstract 633). A second study, in southern Spain, found an HEV seroprevalence of 17.2%; HEV seropositivity was associated with elevated transaminases, and only 1 patient had detectable HEV RNA levels (Abstract 634). These data are a reminder that HEV infection may play a role in HIV-infected patients and should be a consideration in the setting of acute or chronic hepatitis that is not attributable to HBV or HCV infection.

Complications of HIV Infection

Non-AIDS complications, specifically cardiovascular disease (CVD), renal insufficiency, and bone and endocrine disorders persist among patients with treated HIV disease and contribute to morbidity and mortality. Research in this area remains focused on the epidemiology and risk factors for these problems, identifying the contributions of HIV-related immunopathology to specific and collective end-organ diseases, and evaluating interventions to prevent or reduce the morbidity associated with these conditions. CROI

2014 provided new insights into all of these areas.

Evolution of Mortality Due to Non-AIDS Events Over the Past Decade

Between 2000 and 2010, investigators from the Centers for Disease Control and Prevention (CDC) examined causes of death among HIV-seropositive patients aged 30 years to 39 years and 50 years to 69 years, and examined the coefficients of association between HIV and specific non–AIDS-related complications (chronic heart disease, colon cancer, cryptococcal disease, and toxoplasmosis) (Abstract 1019). As expected, the percentage of deaths due to HIV decreased during the 10-year period, particularly among the younger age group. At the same time, the percentage of deaths due to non-AIDS causes rose. In the younger age group the percentage of deaths associated with non-AIDS events increased from 8% in 2000 to 2001 to 12% in 2008 to 2010, and the increase was even greater in the older age group, from 18% to 26%.

In the past decade, the coefficient of association between HIV and specific causes of death rose for heart disease and colon cancer, and fell for cryptococcus and toxoplasmosis. The role of smoking as a contributor to mortality in patients with HIV infection was examined in an analysis of 8 cohorts in Europe and North America (Abstract 1011). Overall mortality rates and deaths due to CVD and non-AIDS malignancies were higher for patients who ever smoked than for those who had never smoked. It was estimated that the years of life lost due to smoking exceeded excess mortality due to HIV infection. These findings highlight the importance of prioritizing chronic disease management and, specifically, smoking cessation activities in the care of HIV-infected adults.

Biomarkers to Predict the Risk of End-Organ Disease and Mortality

Considerable effort has been focused on identifying biomarkers that will help to predict which patients are at highest risk for developing non-AIDS events or for death. The ratio of CD4+ to CD8+ cells has emerged as an important marker of immunodeficiency that is useful in predicting outcomes. Mussini and colleagues found that only 30% of patients among a treated and suppressed cohort with a CD4+ cell count at entry of 378/μL achieved a CD4+ to CD8+ ratio greater than 1. Not surprisingly, younger age and earlier initiation of antiretroviral therapy were associated with normalization of the ratio (Abstract 753). A CD4+ to CD8+ ratio greater than 1 protected against clinical progression to non-AIDS events or death, independent of CD4+ cell count.

Measures of monocyte activation have been shown to be an important contributor to CVD and all-cause mortality in HIV infection.[19-21] Investigators from the SUN (Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy) study examined associations between soluble measures of inflammation and cellular measures of monocyte and T cell activation using immunophenotyping to examine whether cellular activation contributes to levels of soluble markers, after adjustment for clinical factors such as age, sex, CD4+ cell count, viral load, and traditional risk factors (Abstract 755). The investigators found strong associations between greater frequency of CD14+ CD16+ monocytes (activated monocytes) and higher levels of interleukin (IL)-6, D-dimer, and high-sensitivity C-reactive protein (hsCRP), whereas greater frequency of monocytes expressing CC chemokine receptor 2 (CCR2) was associated with lower levels of D-dimer. Higher expression of markers of T cell activation of CD4+ cells (HLA-DR+ CD38+) were associated with higher soluble CD163, whereas markers of CD8+ cell activation were not as strongly associated with soluble measures of inflammation. The causal relationship between these associations cannot be derived from this cross-sectional study, but these findings may help direct future interventional studies.

Coagulation factors are also thought to contribute to the development of non-AIDS events in treated HIV disease. Prior work from the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) group's SMART (Strategies for Management of Antiretroviral Therapy) study has demonstrated that HIV replication is associated with a procoagulant state. At CROI 2014, Baker reported that among treated and suppressed patients, anticoagulant factor levels (factor VII and protein C) were protective against mortality, whereas hepatically produced procoagulant factors (factor V and factor VIII) were associated with increased risk for death (Abstract 756). These findings further support the role of hypercoagulation in the risk for morbidity in the setting of treated HIV disease and the need for further investigation into mechanistic and interventional studies in this area.

In the general population, soluble measures of inflammation are increased among patients with obesity, diabetes, and those who smoke. However, the relationship between these risk factors and measures of inflammation in treated and suppressed HIV patients has not been fully explored. AIDS Clinical Trials Group (ACTG) investigators reported correlations between IL-6, D-dimer, soluble (s) tumor necrosis factor receptor 1 (sTNFR1), gamma interferon–induced protein 10 (IP-10), and sCD14 and metabolic and anthropometric factors (Abstract 757). Increased age, central obesity, smoking, and elevated triglyceride levels were all associated with sCD14, IL-6, and sTNFR1, whereas none of the metabolic or anthropometric measures appeared to correlate to D-Dimer or IP-10.

Data from the SUN study (Abstract 732) found associations between current smoking and higher levels of sCD14, whereas heavy alcohol use was associated with lower D-dimer levels. In a Swiss HIV Cohort study, low to moderate alcohol use—defined as up to 29 grams per day for women and 39 grams per day for men, or approximately 2 drinks per day—was associated with lower rates of CVD (Abstract 731), but whether this benefit is mediated by the effects of alcohol on coagulation warrants further investigation.

The Impact of Antiretroviral Therapy on Inflammatory Biomarkers

It is known that measures of inflammation decline when effective antiretroviral therapy is initiated and plasma HIV RNA level decreases, but how this varies with specific regimens and among subgroups of patients is not yet fully defined. It has also been well documented that women tend to have higher CD4+ cell counts and lower HIV RNA levels than men during early HIV infection, although they progress at a similar rate without treatment. Using samples from a completed international ACTG treatment trial, Mathad and colleagues (Abstract 853) observed that before initiating antiretroviral therapy, women had lower levels of hsCRP and sCD14, and a lower percentage had detectable lipopolysaccharide, and higher levels of endotoxin core antibody (EndoCAb) than men. After 48 weeks of antiretroviral therapy, among those who achieved viral suppression, men had a greater decrease than women in inflammatory markers (tumor necrosis factor [TNF]-α, C-reactive protein [CRP], and sCD14). Whether these differential effects of antiretroviral therapy on measures of inflammation help explain the similar rates of progression to AIDS despite lower viral load, or whether these differential effects contribute to the development of non-AIDS events will require further study. These results underscore the importance of including adequate numbers of women in research of HIV pathogenesis and therapeutics. In this ACTG study, over 50% of subjects enrolled were women.

Studies of measures of inflammation in children also remain limited. Investigators from the ARROW (Antiretroviral Research for Watoto) trial reported changes in inflammatory biomarkers among children with advanced HIV disease treated with antiretroviral therapy (Abstracts 910 and 914) and noted high levels of all markers prior to treatment and rapid declines in IL-6 and CRP after treatment initiation. In contrast, investigators noted a very slow decrease in sCD14 level that seemed to plateau after 24 weeks to 48 weeks and more variable effects on TNF-α level at later time points beyond week 48. Most notable was the observation that levels of inflammatory markers rose among those randomized to stop taking trimethoprim-sulfamethoxazole (TMP-SMX) in this trial, with a persistently higher level of CRP up to 2 years after stopping. The mechanism of the protective effect of TMP-SMX requires further investigation.

CVD

Risk Factors and Rates of CVD

Traditional risk factors for CVD remain prevalent among patients with HIV infection, and several studies at CROI 2014 reported on the contributions of specific risk factor to rates of CVD. Analysis of data from the Veterans Aging Cohort Study (VACS) found that even when traditional risk factors are managed, patients with HIV infection appear to still be at twice the risk for MI compared with HIV-uninfected patients (Abstract 736). A second VACS study demonstrated that HIV is an independent risk factor for CVD among women and, as has been previously noted,[22] that the magnitude of the effect of HIV on this cohort is greater among women (3-fold) than was previously reported among men (1.5- to 2-fold) (Abstract 734). Investigators working with the Partners HealthCare System database reported on rates of major adverse cardiac events during the period from 2000 to 2009 and observed that HIV-infected individuals had higher rates of individual events (MI, stroke, angina, revascularization) and a composite end point that includes all of these diagnoses (Abstract 738). More encouraging news came from Klein and colleagues who reported that patients with HIV infection managed in the Kaiser Permanente California health system from 2010 to 2011 did not have higher rates of MI than those seen in age-matched, HIV-uninfected controls; this occurred despite the higher prevalence of smoking, hypertension, and low high-density lipoprotein (HDL) cholesterol levels among the HIV-infected patients (Abstract 737). Investigators from the multicenter Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort confirmed the importance of Framingham risk score covariates (age, smoking, total and HDL cholesterol, and systolic blood pressure) in predicting MI risk in patients with HIV infection but also found that HIV-associated factors, specifically lower CD4+ cell count and higher level of HIV RNA, remain independent risk factors (Abstract 739), highlighting the important role that immunodeficiency and viral replication may play in the observed increased risk for CVD in HIV infection. Lower CD4+ cell counts were also found to be associated with the risk of ischemic stroke in another report from Kaiser Permanente California investigators (Abstract 741). Finally, work from the MACS (Multicenter AIDS Cohort Study) highlighted the possible contribution of heavy nitrate inhalant use to risk for cardiovascular and renal events (Abstract 740).

Coronary Plaque Associations With Inflammation

At prior CROI meetings, the use of novel imaging methods (computed tomography [CT] angiography to examine features of plaque and ^{18}fluorine-2-deoxy-D-glucose positron emission tomography [^{18}F-FDG-PET] to examine arterial inflammation) for the study of atherosclerosis in HIV disease were discussed.[23] This year 2 groups reported data from further studies employing these methodologies. Zanni, Tawakol, and colleagues (Abstract 130) described the interrelationship between arterial inflammation and high-risk plaque morphology in a study in which participants who had previously undergone CT angiography underwent ^{18}F-FDG-PET and were characterized as having either high or low levels of arterial inflammation (measured from the degree of aortic inflammation over background, known as aortic tissue-to-background ratio [TBR]). Participants with higher levels of aortic inflammation had a higher number of plaques and a greater amount of what is considered to be high-risk morphology

plaque (low attenuation and positive remodeling) than those with lower levels of aortic inflammation. In another study Hsue, Tawakol, and colleagues used ^{18}F-FDG-PET to investigate the relationship between arterial inflammation and splenic and bone marrow activity, hypothesizing that if macrophages contribute to the development of arterial inflammation in HIV, an increase in splenic and bone marrow FDG uptake might be expected (Abstract 131). They found once again that virologically suppressed, HIV-infected patients had higher levels of arterial inflammation than -uninfected controls and higher levels of FDG uptake in spleen and bone marrow but not in muscle tissue, suggesting that immune cell activity may be contributing to this inflammation. Together, these findings suggest a possible link between vascular inflammation and high-risk plaque and, possibly, immune cell activation that warrants further investigation. These findings also highlight the potential use of ^{18}F-FDG-PET scanning as a research tool in studies evaluating potential interventions to reduce the development of atherosclerosis in HIV disease.

Investigators from the MACS presented further evidence supporting the role of monocyte activation in CVD in a cross-sectional study of virally suppressed HIV-infected patients and -uninfected controls who underwent coronary artery calcium scanning and CT angiography (Abstract 730). Among HIV-infected patients, sCD163 but not sCD14 was associated with the presence of coronary plaque (calcified, mixed, and total plaque), whereas in -uninfected patients both markers were associated with plaque. In contrast, T cell activation was higher in the HIV-infected group and was not associated with coronary atherosclerosis in either group.

The contribution of HIV persistence—determined by measurement of ultrasensitive HIV RNA levels (<0.3 copies/mL by single-copy assay) and proviral DNA in peripheral blood mononuclear cells—to endothelial dysfunction was evaluated by University of California San Francisco investigators in a study measuring endothelial function by flow-mediated dilatation (FMD) (Abstracts 727 and 729). In HIV-infected study subjects with low HIV RNA levels, traditional risk factors and cell-associated HIV RNA levels correlated with worsened FMD, raising questions about the role of HIV replication in the pathogenesis of CVD. This issue was further explored in a small pilot study of elite controllers, compared with viremic controllers and noncontrollers, investigating the impact of antiretroviral therapy on FMD (Abstract 729). Twenty-four weeks of antiretroviral therapy resulted in reductions in ultrasensitive HIV RNA levels in the elite controllers and an improvement in T cell activation. However, FMD did not improve in the small sample evaluated; given the known variability of FMD, these pilot data support further investigation into the role of HIV persistence in the pathogenesis of vascular disease.

Heart Failure

Growth stimulation–expressed gene 2 (ST2; a member of the IL-1 receptor family) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), biomarkers of cardiac dysfunction that are predictive of heart failure and mortality in the general population, were previously reported to be higher in patients with HIV infection and associated with mortality.[24] These findings were extended by data confirming that higher mortality was predicted by NT-proBNP levels among women with HIV infection (Abstract 723) and by a study that demonstrated that ST2 and growth differentiation factor 15 (GDF-15), which is involved in regulating inflammation, were independent predictors of mortality and, in the case of ST2, diastolic dysfunction (Abstract 725). The clinical role of these biomarkers remains to be determined. Cardiac steatosis, measured by magnetic resonance spectroscopy, was shown to be 38% higher in HIV-infected patients than in -uninfected controls. Among HIV-infected patients, female sex and higher amounts of visceral fat were associated with increased cardiac steatosis (Abstract 724).

Lipids, CVD Risk, and Antiretroviral Therapy

There are numerous species of lipids that can be measured in plasma using mass spectrometry, and changes in the lipidome have been used to stratify patients' future cardiovascular risk. Data on lipid profiles were reported by Australian investigators. They noted adverse lipid profiles in patients randomized to either efavirenz- or atazanavir/r-based regimens (Abstract 742) and the ability of plasma lipid profiling to identify patients at higher risk for coronary artery disease events in a case-control study (Abstract 748).

The association between recent abacavir use and risk for MI remains controversial. Investigators from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study reported a decline in the use of abacavir among patients at high and moderate risk for CVD since the association between abacavir and MI was first reported in 2008.[25] They note that the association between abacavir use and MI persists in more recent years, despite this change in prescribing patterns. (Abstract 747LB). One potential mechanism to explain the link between abacavir and MI is changes in platelet function after abacavir exposure. Using samples from the SWIFT study, in which patients were randomized to switch from abacavir and lamivudine to tenofovir and emtricitabine or to remain on abacavir and lamivudine, O'Halloran and colleagues (Abstract 749LB) measured changes in markers of platelet activation in the 2 groups and found an increase in soluble glycoprotein VI (sGPVI) among those who switched from abacavir- to tenofovir-based treatment, whereas no changes in soluble P-selectin were observed. It remains to be clarified whether this change in platelet function could contribute to MI risk during abacavir-based therapy.

Fat

Obesity remains an important problem that contributes to other comorbidities, including hypertension and

CVD, and complicates the management of HIV disease. Not surprisingly, a body mass index (BMI) of 30 kg/m^2 or higher was a risk factor for developing hypertension in a study of South Africans initiating antiretroviral therapy (Abstract 759). Lower pre–anitretroviral therapy CD4+ cell count and female sex were risk factors for developing obesity among 3000 treatment-naive patients followed in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort (Abstract 802). A higher rate of mortality 48 months after initiation of antiretroviral therapy was observed in obese (BMI ≥ 30 kg/m^2) South African subjects than in those with normal BMIs (18 kg/m^2-24.9 kg/m^2); however, loss to follow-up was lower in the obese group than in the group with normal BMIs (Abstract 803).

Tesamorelin, a synthetic growth hormone–releasing hormone agonist, has been FDA approved for the treatment of HIV-related lipodystrophy. Grinspoon and colleagues reported the effects of tesamorelin on hepatic fat in a randomized, placebo-controlled trial conducted in HIV-infected patients who had evidence of abdominal fat accumulation. After 6 months of treatment with subcutaneous tesamorelin 2 mg, compared with placebo, visceral adipose tissue and hepatic lipid measurements decreased substantially (Abstract 135). Whether tesamorelin can reduce hepatic steatosis remains to be demonstrated but seems very important to investigate given the currently limited available treatment options for this condition.

Statins

There continues to be great interest in the role of statin drugs in the management of HIV-related cardiovascular risk. Several new developments from ongoing clinical trials of statin use in HIV-infected patients were reported this year. Rosuvastatin was previously shown to reduce low-density lipoprotein (LDL) cholesterol and measures of monocyte immune activation in HIV-infected patients.[26,27] At CROI 2014, McComsey and colleagues reported a decline in oxidative LDL with rosuvastatin treatment (Abstract 134); however, this did not correlate with reductions in other markers of inflammation. In addition, they reported an increase in total hip and trochanter BMD among SATURN-HIV (Stopping Atherosclerosis and Treating Unhealthy Bone With Rosuvastatin in HIV) trial participants randomized to receive rosuvastatin. However, markers of insulin resistance also worsened substantially in this group, with 1 subject developing diabetes. These findings suggest that rosuvastatin use in patients with HIV should include monitoring for diabetes. The 52-week results of the INTREPID study of pitavastatin 4 mg compared with pravastatin 40 mg showed the continued superiority of pitavastatin in lowering LDL at 52 weeks of follow-up; safety appeared similar in both study groups, and there were no reports of diabetes (Abstract 751LB).

Pulmonary Disease

A Themed Discussion session at CROI 2014 focused on pulmonary disease, and results from ongoing cohort studies aimed at investigating the relationship between HIV and lung diseases were showcased. Investigators from the ALIVE (AIDS Linked to the Intravenous Experience) study reported that HIV infection was independently associated with increased risk of acute exacerbations of chronic obstructive pulmonary disease (COPD) (Abstract 773), and the ANRS (Agence Nationale de Recherche sur le Sida et les Hépatites Virales) HIV CHEST study identified a high prevalence of COPD among HIV-infected patients, with marijuana use as a possible risk factor (Abstract 776). EXHALE (Examinations of HIV-Associated Lung Emphysema) investigators noted an association between HIV infection and decline in lung function that appeared to be mediated by elevations in sCD14 levels in HIV-infected subjects (Abstract 774), and an association between HIV infection and the development of emphysema (Abstract 775).

Renal Disease

The long-term outcomes after development of chronic renal impairment on antiretroviral therapy have not been well described in prior studies. D:A:D investigators performed a detailed analysis of the outcomes of participants who had a confirmed decline in estimated glomerular filtration rate (≤70 mL/min/1.73 m^2) (Abstract 792). After the development of renal impairment while on antiretroviral therapy, 23% of patients improved, 69% stabilized, and 7.8% worsened. Older age, diabetes, and the use of tenofovir or ritonavir-boosted PIs were associated with a lower chance of improvement, but there was some evidence that discontinuation of tenofovir before the development of chronic renal impairment was associated with better outcomes. A chronic kidney disease risk score reported by Scherzer and colleagues that incorporates traditional risk factors for renal disease (age, glucose levels, systolic blood pressure, hypertension, triglyceride levels, and proteinuria) may prove useful in identifying patients in whom tenofovir use should be avoided (Abstract 798). Genetic markers for tenofovir proximal tubular dysfunction were also reported (Abstract 799).

Immune complex kidney disease (ICKD) has been less studied than HIV-associated nephropathy HIVAN. Investigators from the UK demonstrated that HIV viremia was a risk factor for ICKD and, compared with HIVAN, ICKD was associated with less advanced immunodeficiency; black race remained a strong risk factor for both ICKD and HIVAN (Abstract 793).

Bone

Examination of the risk factors and pathogenesis of bone loss in HIV disease remains an important area of investigation. At CROI 2014, more information on possible interventions to prevent or treat bone loss was presented.

The finding that HIV infection early in life appears to be associated with replicative senescence and lower

numbers of bone precursor cells was reported by Yin and colleagues from a study that included perinatally HIV-infected men compared with -uninfected men (Abstract 132).

Data from 2 CDC cohort studies demonstrated that in HIV-infected patients, low BMD (measured by dual-energy x-ray absorptiometry [DXA] scans) and older age were associated with the risk of future fracture (Abstract 781). These data confirm the utility of DXA scans for predicting fracture risk in patients with HIV infection. Concurrent use of daily calcium (1000 mg of calcium carbonate) and vitamin D (4000 IU of vitamin D_3) supplements in patients starting treatment with efavirenz, tenofovir, and emtricitabine mitigated the loss of hip BMD in a placebo-controlled ACTG trial (Abstract 133). Treatment was safe and well tolerated and is something that can be incorporated into clinical practice for patients who initiate this antiretroviral regimen. In another ACTG trial, 96-week BMD losses in lumbar spine and total hip were statistically significantly lower among patients randomized to receive raltegravir than among those randomized to receive atazanavir/r or darunavir/r (Abstract 779LB). Finally, a small, randomized pilot study suggested that biennial doses of zoledronic acid in HIV-infected patients may provide a similar benefit to annual administration of the drug in improving BMD (Abstract 782).

Frailty and Aging

Geriatric syndromes were reported to be more common among HIV-infected patients than among -uninfected controls in several studies (Abstracts 766 and 767). Immunologic profiles that have been developed for the study of aging are being increasingly applied to populations of patients with HIV infection. Ndumbi and colleagues examined the prevalence of the immune-risk phenotype that predicts mortality in elderly individuals in a group of successfully treated HIV-infected patients. They found a higher prevalence of features of the immune-risk phenotype in the HIV-infected group than in -uninfected controls (Abstract 765). In addition, they noted that within the HIV-infected group, median telomere length was shorter, although it did not reach statistical significance.

Investigators from the ALIVE cohort applied a validated index that measures inflammation and predicts the risk of mortality among adults aged older than 65 years to a population of HIV-infected patients and examined whether measures of inflammation added to the predictive value of a frailty index. The inflammatory index included measurement of IL-6 and sTNFR1 levels and frailty measurement included the presence of 3 or more of the following: weakness, slow gait, weight loss, low physical activity, and exhaustion. Investigators found strong associations between measures of inflammation and the presence of frailty. However, in models, controlling for sociodemographic characteristics, comorbidity, HIV infection, and frailty, the inflammatory index remained statistically significantly associated with mortality (Abstract 762). These results suggest that interventions to reduce inflammation in the setting of treated HIV infection may have the potential to improve long-term outcomes. One such intervention may be exercise. Longo and colleagues demonstrated that moderate-intensity exercise (walking, with or without strength exercises, 3 times/week) improved aerobic fitness, metabolic markers, and measures of inflammation in antiretroviral therapy–treated HIV infection (Abstract 763).

Kaposi Sarcoma

HIV PIs—Effect on Clinical Kaposi Sarcoma?

HIV PIs exhibit antiangiogenesis and antiviral activity against Kaposi sarcoma (KS)-associated herpesvirus (KSHV) in vitro, but the clinical relevance of these observations is unknown. Chiao and Kowalkowski examined clinical KS infection risk in a cohort of 25,529 US veterans receiving combination anitretroviral therapy. There was a 4% reduction in risk for new KS infections among those receiving a PI- compared with risk among those on a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; KS infection risk for the subset of patients receiving nelfinavir- was actually 4% higher than for those receiving NNRTI-based regimens (Abstract 708). Martin and colleagues evaluated clinical outcomes among Ugandan patients with KS in a randomized study comparing lopinavir/r- with efavirenz-based antiretroviral therapy (Abstract 710). The 224 patients enrolled had clinical evidence of KS but did not yet meet the clinical indications for chemotherapy according to Ugandan guidelines; however, many patients had very extensive cutaneous disease. At 1 year, there was no difference between study arms in death or disease progression, and the 1-year mortality rate for the cohort was 18%. Despite the biologic plausibility of HIV PIs in prevention or treatment of KSHV disease, these studies suggest that treatment with HIV PIs is not more beneficial than treatment with NNRTIs in patients with KS. The alarming mortality rates for KS in the Ugandan study call for more intensive treatment for these patients.

KICS

KSHV inflammatory cytokine syndrome (KICS) is a newly described clinical syndrome characterized by multiorgan KSHV-associated tumors and elevated cytokines that is distinct from classic HIV-associated KS, primary effusion lymphoma, or multicentric Castleman disease. Polizzoto and colleagues extended prior descriptions of this syndrome by comparing 10 patients meeting KICS criteria with KSHV/HIV-coinfected patients and HIV-monoinfected patients with or without virologic suppression (Abstract 101). The patients with KICS had, in addition to greater multiorgan involvement, higher levels of anemia, leukopenia, thrombocytopenia, CRP, IL-6, and IL-10 than the comparator groups. Six of the 10 patients with KICS died despite treatment. This report highlights the high level of morbidity and mortality

associated with KICS and the need for new therapeutic approaches.

Tuberculosis

New data on novel drugs and combinations for the treatment of tuberculosis (TB), patient outcomes using new rapid TB diagnostics, and a short-course TB prevention strategy were among the highlights of CROI 2014. In the TB symposium (Session S4), Murray showcased the genetics and pathogenesis of TB drug resistance mutations (Abstract 107), Karakousis challenged the current concept of TB latency (Abstract 108), Barry proposed high-tech imaging methods (PET and CT) to understand TB response during new drug development (Abstract 109), and Godfrey-Faussett offered population-based strategies for control of HIV-related TB (Abstract 110).

New TB Drugs and Shorter Regimens—Combining and Defining Activity

New TB drugs are being combined to evaluate potency and prospects for treatment shortening. Bedaquiline, an inhibitor of adenosine triphosphate (ATP) synthetase, has already been FDA approved for use in treatment of drug-resistant TB, and the investigational drug PA-824, a cell wall inhibitor, shows strong anti-TB activity in short-term studies in humans. Studies of animal models suggest that combining these 2 agents with a third drug such as pyrazinamide or clofazimine achieves rapid and sterilizing responses. Diacon and colleagues presented the results of a 7-arm study evaluating the use of pyrazinamide or clofazimine alone or in combination with PA-824 and bedaquiline (Abstract 97LB). One hundred five subjects with smear-positive TB were enrolled in this 14-day study. The primary end point was early bactericidal activity (EBA). The 3-drug combination of PA-824, bedaquiline, and pyrazinamide showed an EBA of 0.167 (95% confidence interval [CI], 0.078, 0.256), similar to a standard 4-drug TB regimen (EBA 0.151; 95% CI, 0.70, 0.231). This combination will be studied on a larger scale for longer durations. Clofazimine showed no activity in this study when administered alone, nor any additional activity when combined with PA-824, bedaquiline, and pyrazinamide. Although some argue that 2 weeks is an insufficient time period to observe the activity of clofazimine, others interpret these data as strong evidence that clofazimine adds only toxicity and not activity to TB treatment.

Moxifloxacin and Rifapentine in Combination

Moxifloxacin and rifapentine, both of which are efficacious in combination TB treatment, are being evaluated for use in treatment-shortening regimens. Dorman and colleagues presented the results of a phase II study of patients randomized to receive a standard 4-drug TB regimen (isoniazid, rifampin, ethambutol, and pyrazinamide) compared with an investigational regimen of moxifloxacin, rifapentine, ethambutol, and pyrazinamide (Abstract 93). This was a "double-switch" study in which isoniazid and rifampin were replaced with moxifloxacin and rifapentine. Rifapentine was dosed at 7.5 mg/kg daily. The proportion of patients with culture conversion using solid media after the induction phase was similar in the 2 arms (85% in the investigational arm vs 86% in the control arm). Higher rates of culture conversion were achieved on liquid media in the investigational arm than in the control arm (85% vs 69%, respectively; $P = .08$). Four patients in the investigational arm and 2 patients in the control arm changed therapy because of toxicity. Investigators concluded that this investigational TB regimen is safe, well tolerated, and efficacious and that these data support the evaluation of rifapentine- and moxifloxacin-containing regimens for treatment shortening in a larger phase III study.

HIV and TB Drug Interactions—More Data and More Options

As new drugs become available for prevention and treatment of TB, it is essential that potential drug interactions are understood in order to avoid jeopardizing efficacy or patient safety of TB or HIV treatment during cotreatment of HIV and TB. In an ongoing study of TB prevention regimens, specifically a 1-month course of rifapentine (10 mg/kg) and isoniazid (300 mg) compared with 9 months of isoniazid alone, investigators reported the effect of rifapentine, a cytochrome P450 inducer, on efavirenz exposure (Abstract 105). Clearance of efavirenz in the presence or absence of rifapentine was equivalent, providing reassurance that these drugs can be safely coadministered at these doses. For TB treatment, Reynolds and colleagues reported results of an intensive pharmacokinetic study, which suggests that the raltegravir dose should be doubled from 400 mg to 800 mg twice daily in persons receiving thrice-weekly rifampin, in order to achieve raltegravir drug exposure levels comparable to those seen in persons not receiving rifampin (Abstract 496). This study did not include viral load data; however, results are similar to those from other studies that have examined interactions between daily rifampin and raltegravir.

Xpert MTB/RIF Assay—Rollout in South Africa Hits Road Bumps

In 2010, the World Health Organization endorsed a rapid combined TB and resistance to rifampicin assay (Xpert MTB/RIF) as a first-line test for TB diagnosis.[28] This molecular-based assay has a sensitivity that exceeds the routine smear for acid-fast bacilli (AFB), provides a readout in approximately 2 hours, and can detect most cases of rifampin resistance. In 2011, South Africa made the bold policy move of replacing the routine AFB smear with Xpert MTB/RIF as the first-line diagnostic test for patients with suspected TB. The South African government and donors equipped central laboratories with hundreds of new machines in a phased implementation plan. Churchyard, Fielding, and colleagues presented early readouts from the rollout of this much anticipated new technology (Abstracts 95 and 96LB).

The XTEND study, a pragmatic, cluster-randomized trial, addressed the following questions: Were more cases of TB detected with access to the Xpert MTB/RIF assay? Did more patients diagnosed with TB start TB therapy? Was there any reduction in TB-associated mortality? In this study, 20 laboratories were randomized to immediate or delayed access to Xpert MTB/RIF. Patients from 2 primary health centers served by these labs were approached for enrollment in this TB screening evaluation study. Patients attending clinics in the immediate access arm were evaluated for TB with the Xpert MTB/RIF test. Patients attending clinics in the delayed access arm were evaluated with routine AFB smear. There were 4412 evaluable laboratory tests. The yield for TB diagnosis was higher with Xpert MTB/RIF use (9.2%) than with AFB smear (7.8%). In their model, Xpert MTB/RIF testing increased yield of TB detection by 49%. However, there was no difference between the groups in terms of number of persons started on TB therapy (10.8% for the Xpert MTB/RIF arm vs 12.5% for the routine AFB smear arm). Likewise, mortality did not differ between the 2 arms (3.9% in the Xpert MTB/RIF arm vs 5.0% in the routine AFB smear arm). Among persons self-reported as HIV infected, mortality was lower with use of Xpert MTB/RIF (5.6%) compared with controls (1.6%).

The major conclusion from this study was that scaling up new interventions like the Xpert MTB/RIF assay requires strengthening and coordination of health systems to reach maximal benefit. In the XPERT study, test results from both Xpert MTB/RIF tests and AFB smears were returned to the provider in an average of 2 days. Providing the results of new TB diagnoses to patients fell short of targets and subsequent steps, such as the initiation of antiretroviral therapy for HIV-infected persons, were also often not done in a timely fashion. According to Churchyard, the South African government was disappointed with the findings, but remains supportive of the Xpert MTB/RIF assay for first-line TB diagnosis and is designing a corrective plan for health care system deficiencies.

Urinary Lipoarabinomannan Assay—High Yield in Hospitalized Patients in South Africa

TB is often undiagnosed and a cause of mortality in African patients with advanced AIDS. Disseminated TB has nonspecific symptoms and smear tests may be positive in less than half of cases. Last year, studies presented at CROI showed that the rapid, low cost, lateral flow, point-of-care, urinary lipoarabinomannan (LAM) test is a valuable diagnostic tool for patients with low CD4+ cell counts. This year, Lawn and colleagues reported the performance of urinary LAM testing among adult HIV-infected patients admitted to a district hospital in South Africa (Abstract 811LB). Sputum, blood, and urine exams were sent within 24 hours of admission for all adult HIV-infected patients. After excluding those with a known TB diagnosis, 139 of 427 patients were diagnosed with TB. Adding urinary LAM testing to Xpert MTB/RIF testing increased rapid detection from 26.6% to 80.6%, and urinary LAM testing detected 85% of TB cases in persons with CD4+ cell counts below 100/μL. Urinary LAM testing detects disseminated TB, and in regions like South Africa where TB rates are extraordinarily high, screening all ill, HIV-infected patients who require hospitalization for TB using both Xpert MTB/RIF and LAM assays makes good sense. Rapid TB and the initiation of antiretroviral therapy in these patients could have a high impact on mortality.

Short-Course TB Prevention

Three months of once-weekly rifapentine plus isoniazid (900 mg) is comparable to 9 months of daily isoniazid (300 mg) for TB prevention and is now a recommended option by the CDC.[29] However, it is unknown whether this short-course regimen provides the same protection to HIV-infected persons as longer treatment with isoniazid alone. Sterling and colleagues presented data from analysis of the 399 HIV-infected persons enrolled in the randomized trial that was the basis for the new recommendation on short-course preventive TB therapy (Abstract 817). Participants were followed for 33 months and the noninferiority margin was 0.75%. Regimen completion rate was higher in the short-course treatment arm (88%) compared with the standard treatment arm (64%). There were only 8 cases of TB total, and the cumulative rates of TB were similar between the 2 arms (1.01% in the short-course arm vs 3.69% in the standard arm). Drug discontinuations were low and rates were similar between the arms (3.4% in the short-course arm vs 4.2% in the standard arm). The overall number of TB cases was low in this study, reflecting the epidemiology of TB in this population. Nevertheless, the study provides reassurance that a short-course, once-weekly regimen can be safely used in HIV-infected patients.

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A list of all cited abstracts appears on pages 632-638 of this issue. Abstracts are published in *Top Antivir Med.* 2014;22(e-1):1-570, a special online issue available at www.iasusa.org/pub.

Additional References

1. Zeuzem S, Dusheiko GM, Salupere R. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. *Hepatology*. 2013;58(S1):733A-734A.
2. AbbVie. AbbVie completes largest phase III program of an all-oral, interferon-free therapy for the treatment of hepatitis C

genotype 1 [press release]. http://abbvie.mediaroom.com/2014-01-31-AbbVie-Completes-Largest-Phase-III-Program-of-an-All-Oral-Interferon-Free-Therapy-for-the-Treatment-of-Hepatitis-C-Genotype-1. Accessed on March 31, 2014.

3. Lawitz E, Vierling J, Murillo A, et al. High efficacy and safety of the all-oral combination regimen, MK-5172/MK-8742 + /- RBV for 12 weeks in HCV genotype 1 infected patients: the C-WORTHY study. 24th Conference of the Asian Pacific Association for the Study of the Liver. March 12-15, 2014; Brisbane, Australia.
4. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA*. 2013;310(8):804-811.
5. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with Peginterferon and Ribavirin Leads to High Rates of SVR in Patients with HCV Genotype 1 Who Relapsed After Previous Therapy: a Phase 3 Trial. *Gastroenterology*. 2014;[Epub ahead of print].
6. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology*. 2014; 146(2):430-441.
7. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: The randomized PILLAR study. *Hepatology*. 2013; 58(6):1918-1929.
8. Janssen Therapeutics. Simeprevir [package insert]. 2013.Titusville, NJ, Janssen Therapeutics.
9. Jacobson IM, Ghalib RH, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: The COSMOS study. *Hepatology*. 2013;58(6):1379A-1380A.
10. Ferenci P, Asselah T, Foster GR, et al. 1416 Faldaprevir plus pegylated interferon alfa-2a and ribavirin in chronic HCV genotype-1 treatment-naïve patients: Final results from STARTVerso1, a randomised, double-blind, placebo-controlled phase III trial. *J Hepatol*. 2013;58(Supp 1): S569-S570.
11. Jensen DM, Asselah T, Dieterich DT, et al. A pooled analysis of two randomized, double-blind placebo-controlled phase III trials (STARTVerso1&2) of faldaprevir plus pegylated interferon alfa-2a and ribavirin in treatment naive patients with chronic hepatitis C genotype-1 infection. *Hepatology*. 2013;58(S1):734A-735A.
12. Heidrich B, Yurdaydin C, Kabacam G, et al. Late HDV RNA relapse after peginterferon alfa-based therapy of chronic hepatitis delta. *Hepatology*. 2014;[Epub ahead of print].
13. Abbas Z, Memon MS, Mithani H, Jafri W, Hamid S. Treatment of chronic hepatitis D patients with pegylated interferon: a real world experience. *Antivir Ther*. 2014;[Epub ahead of print].
14. Crum-Cianflone NF, Curry J, Drobeniuc J, et al. Hepatitis E virus infection in HIV-infected persons. *Emerg Infect Dis*. 2012; 18(3):502-506.
15. Renou C, Lafeuillade A, Cadranel JF, et al. Hepatitis E virus in HIV-infected patients. *AIDS*. 2010;24(10):1493-1499.
16. Kaba M, Richet H, Ravaux I, et al. Hepatitis E virus infection in patients infected with the human immunodeficiency virus. *J Med Virol*. 2011;83(10):1704-1716.
17. Keane F, Gompels M, Bendall R, et al. Hepatitis E virus coinfection in patients with HIV infection. *HIV Med*. 2012;13(1):83-88.
18. Maylin S, Stephan R, Molina JM, et al. Prevalence of antibodies and RNA genome of hepatitis E virus in a cohort of French immunocompromised. *J Clin Virol*. 2012;53(4):346-349.
19. Crowe SM, Hoy JF. Are monocytes the canary in the coal mine for HIV-related atherosclerosis? *J Infect Dis*. 2012;206(10):1491-1493.
20. Funderburg NT, Zidar DA, Shive C, et al. Shared monocyte subset phenotypes in HIV-1 infection and in uninfected subjects with acute coronary syndrome. *Blood*. 2012;120(23):4599-4608.
21. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis*. 2011;203(6):780-790.
22. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92(7):2506-2512.
23. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. *JAMA*. 2012;308(4):379-386.
24. Secemsky E, Scherzer R, Nitta E et al. ST2 and NT-proBNP are associated with cardiac dysfunction and mortality in HIV + individuals [Abstract 749]. 20th Conference on Retroviruses and Opportunistic Infections (CROI). March 3-6, 2013; Atlanta, Georgia.
25. Strategies for Management of Antiretroviral Therapy/INSIGHT, D:A:D Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22:F17-F24.
26. McComsey G, Jiang Y, Debanne S et al. Effect of statins on immune activation and inflammation in HIV+ subjects on ART: a randomized placebo controlled trial [Abstract 186LB]. 20th Conference on Retroviruses and Opportunistic Infections (CROI). March 3-6, 2013; Atlanta, Georgia.
27. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis*. 2014;58(4):588-595.
28. World Health Organization (WHO). WHO endorses new rapid tuberculosis test: a major milestone for global TB diagnosis and care. http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/. Accessed on April 11, 2014.
29. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166.
30. Asselah T, Marcellin P. Interferon free therapy with direct acting antivirals for HCV. *Liver Int*. 2013;33 (Suppl 1):93-104.

Top Antivir Med. 2014;22(2):602-615