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Jürgen Rockstroh, MD, is Professor of Medicine and Head of the HIV Outpatient Clinic at the University of Bonn in Germany. He earned a Doctor of Medicine degree from the Rheinische Friedrich-Wilhelms University of Bonn, and completed his residency in the Department of Medicine also at the University of Bonn. His department treats the world's largest cohort of HIV-infected hemophiliacs.

In addition to his clinical practice, Dr. Rockstroh is involved in HIV research on: antiretroviral therapy, including new drug classes; the course of HIV disease in haemophiliacs; and HIV and hepatitis co-infection.

He has been an investigator in multiple clinical trials of antiretroviral agents and treatments for HIV and hepatitis co-infection. An active member of the HIV/AIDS treatment community, Dr. Rockstroh was the Chairman of the German Clinical AIDS Working Group (KAAD) from 1998 to 2007. From 2007 to 2011, he was elected as the president of the German AIDS Society.

He has also been since 2009 a member of the executive committee of the European AIDS Clinical Society (EACS). He chaired the organizing committee for the First and Second International Workshops on HIV and Hepatitis Co-Infection in 2004 and 2005 in Amsterdam, and was on the international organizing committee for the First European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Co-Infected Patients in 2005. He was co-chair of the EACS conference in Cologne in 2009.

Dr Rockstroh was a member of the CCC for the WAC in Vienna in 2010. He currently chairs the hepatitis research activities in NEAT and EuroSIDA.

The German Society for Infectious Diseases awarded Dr.

Rockstroh and his co-authors the prize in clinical infectious disease in 2002 and national AIDS research prize in 2005. Dr Rockstroh has authored or co-authored over 300 publications in peer-reviewed journals, and over 70 book chapters.

"For me the most compelling news from CROI were on the one hand, that cure rates under modern HCV therapy for HIV/HCV co-infected patients were similar to HCV mono-infected patients, suggesting that we no longer need to separate between HIV/HCV co-infected and HCV-mono-infected patients. Indeed, we will need to fight for inclusion of co-infected individuals into the regular mono-infection trials as there is no reason to longer think, that these patients respond less favourably than the ones with hepatitis C alone. The other exciting news were clearly from the NIH study looking at the efficiency of various triple DAA combinations, indicating that it will be possible to treat the majority of patients with even shorter treatment durations of only 6 weeks. The combination of Sofosbuvir and Ledipasvir in combination with either GS9669 (non nucleoside NS5B inhibitor) or in combination with GS-9451 (a protease / NS3/4 inhibitor) were both highly successful and cured almost all patients in only 6 weeks. Hopefully, shorter treatment durations will also come with a reduction in costs and allow more patients to be set on therapy. Clearly, the DAA combination era is about to arrive promising Interferon and Ribavirin free treatments for all. It is now time to make sure that all our patients have been tested for possible HCV infection in order to be able to treat all patients accordingly when these very safe and efficient regimens become available".

Six or 12 weeks of therapy with three oral direct-acting antivirals (DAAs) for HCV genotype 1 (HCV-1) infection yielded 95% or higher sustained virologic response rates 12 weeks after treatment ended in treatment-naive inner-city patients with hard-to-treat HCV infection. Almost everyone had an undetectable HCV load at the end of 6 or 12 weeks of treatment with an assay that measures HCV RNA levels down to 12 IU/mL. Researchers from the National Institutes of Health and collaborating centers in the Washington-Baltimore area proposed that their findings offer "a new paradigm of combination therapy to reduce HCV treatment duration, which may be vital to the treatment and eradication of HCV globally." SYNGERY involved double- or triple-DAA combinations given for 6 or 12 weeks to treatment-naive HCV-1 patients consecutively enrolled in three arms of this phase 2 prospective cohort study. No one had HIV-1 infection. The base combination included sofosbuvir (a nucleotide NS5B polymerase inhibitor) and ledipasvir (an NS5A inhibitor) in a once-daily fixed-dose combination (FDC). Arm A participants took FDC for 12 weeks. Arm B participants took FDC plus GS-9669, a once-daily nonnucleoside NS5B inhibitor, for 6 weeks. Arm C enrollees took FDC plus GS-9451, a once-daily HCV NS3/4 protease inhibitor, for 6 weeks. Each arm had 20 participants. No one in arm B or C could have cirrhosis; arm A participants could have any fibrosis stage. Most study participants (88%) were African American, men (72%), and infected with genotype 1a (70%). Most had an HCV load above 800,000 IU/mL (70%), and most had an IL28B non-CC genotype (82%), which is associated with lower chances of responding to interferon/ribavirin. Stage 3 or worse fibrosis affected 35% in arm A, 25% in arm B, and 25% in arm C. None of these variables differed significantly between arms. In an intention-to-treat analysis, everyone in arm A, 75% in arm B, and 95% in arm C had an end-of-treatment viral load below 12 IU/mL. With an assay limit of 43 IU/mL, everyone in every arm had an undetectable HCV load at the end of treatment. Everyone in arm A had a sustained virologic response for 12 weeks after completing therapy (SVR12), as did 95% in arm B and 100% in arm C. All told, 39 or 40 participants in this hard-to-treat population attained SVR12 after 6 weeks of treatment with triple-DAA therapy. Everyone taking two DAAs for 12 weeks reached SVR12. Viral decay was significantly faster with the

triple combinations than with the double combinations. No one stopped treatment, and there were no grade 4 adverse events or serious adverse events related to study medication. There were two grade 3 adverse events--pain related to post-treatment liver biopsy and vertigo in a patient with a history of severe intermittent vertigo. Alanine aminotransferase levels dropped to normal after 2 weeks of treatment in 90% in arm A, 100% in arm B, and 95% of arm C. Grade 3 abnormalities developed during treatment in 15% in arm A, 10% in arm B, and 20% in arm C. The SYNERGY team concluded that, "in this inner city patient population addition of a third antiviral agent allowed successful eradication of HCV in 6 weeks in a difficult to treat patient population." Sofosbuvir, a direct-acting antiviral active against HCV genotypes 1 through 6, produced high 12- or 24-week sustained virologic responses (SVRs) in HCV-treatment-naive and experienced people with HIV coinfection. A nucleotide HCV polymerase inhibitor, sofosbuvir has been licensed for treatment of chronic HCV infection in people with or without HIV. In people without HIV infection, sofosbuvir plus ribavirin has yielded high SVRs in people infected with HCV genotypes 1, 2, and 3. To test the efficacy and safety of this regimen in people with HIV, researchers conducted the PHOTON-1 study. The trial had three arms: arm GT1-N enrolled 114 HCV treatment-naive people with genotype 1 who took sofosbuvir plus ribavirin for 24 weeks, arm GT2/3-N had 68 treatment-naive people with genotype 2 or 3 who took the same regimen for 12 weeks. In Arm GT2/3-E 41 treatment-experienced genotype 2 or 3 patients took sofosbuvir plus ribavirin for 24 weeks. Participants could have cirrhosis, with no platelet cutoff. They could be taking antiretrovirals (with a viral load below 50 copies and a CD4 count above 200) or not taking antiretrovirals (with a CD4 count above 500). The primary endpoint was SVR12, an undetectable load 12 weeks after treatment ends as measured by an assay with a lower limit of 25 IU/mL. Across the three treatment groups, GT1-N, GT2/3-N, AND GT2/3-E, age averaged 48, 49, and 54; 82%, 81%, and 90% were men; and 32%, 12%, and 17% were black. Ninety people (79%) in the GT1-N arm had genotype 1a. Proportions with the favorable IL28B CC genotype was 27% in GT1-N, 37% in GT2/3-N, and 49% in GT2/3-E. Respective proportions with cirrhosis were 4%, 10%, and 24%, and proportions on antiretroviral therapy 98%, 90%, and 95%. Mean CD4 counts were 636, 585, and 658. Discontinuations numbered 11 (10%) in arm GT1-N, 6 (9%) in GT2/3-N, and 1 (2%) in GT2/3-E. Respective withdrawals for adverse events were 3 (3%), 3 (4%), and 1 (2%). One person in GT1-N stopped treatment for lack of efficacy. End-of-treatment (EOT), SVR12, and SVR24 among treatment-naive people were all 67% or higher:

- Genotype 1 naive: EOT 100%, SVR12 76%, SVR24 75%
- Genotype 2 naive: EOT 96%, SVR12 88%, SVR24 88%
- Genotype 3 naive: EOT 98%, SVR12 67%, SVR24 67%

Among treatment-naive people, HCV virologic failure rates were 23% with genotype 1, 4% with genotype 2, and 29% with genotype 3. Respective relapse rates were 22%, 0%, and 29%. Among treatment-experienced people, 92% with genotype 2 and 94% with genotype 3 attained SVR12. HCV virologic failure rates were 4% with genotype 2 and 6% with genotype 3 for treatment-experienced people. Respective relapse rates were 4% and 6%. Deep sequencing revealed no resistance mutations in people with virologic failure. Grade 3 or 4 adverse events arose in 10% of patients treated for 12 weeks and in 12% treated for 24 weeks. Respective serious adverse event rates were 7% and 6% and discontinuations for adverse events 4% and 3%. There was one death, a suicide, in a person with a history of depression who was being treated for attention deficit hyperactivity disorder and insomnia. Grade 3 or 4 lab abnormalities arose in 12% of people treated for 12 weeks and 21% treated for 24 weeks. Hemoglobin levels below 10 mg/dL were recorded in 10% treated for 12 weeks and 17% treated for 24 weeks. But one only 1 person in each treatment duration group had a hemoglobin below 8.5 mg/dL. Two people had transient HIV RNA breakthroughs, both with documented nonadherence to their antiretrovirals. CD4 percent did not drop with treatment. Absolute CD4 counts did fall, probably reflecting the well-appreciated lymphocyte decline with ribavirin. Twelve weeks of a regimen containing three direct-

acting antivirals (DAAs) that may become the first anti-HCV triple coformulation produced sustained virologic response rates above 90% through 12 weeks after treatment ended (SVR12). The 166-person study had 11 virologic failures (6.6%), all in people with HCV genotype 1a. The combination includes daclatasvir (an NS5A replication complex inhibitor), asunaprevir (an NS3 protease inhibitor), and BMS-791325 (a nonnucleoside NS5B polymerase inhibitor). Because the three-drug regimen produced high SVR12s in HCV-infected people without cirrhosis, researchers extended that study to include patients with cirrhosis. Although daclatasvir can be dosed once daily, all three drugs were given twice daily in this trial, with an eye toward a developing a twice-daily fixed-dose triple combination. The primary endpoint was SVR12 with response determined by an assay that has a lower limit of 25 IU/mL. The only difference between the two study arms was the dose of BMS-791325, 75 or 150 mg. Eighty people got randomized to 75 mg and 86 to 150 mg. All 166 study participants were treatment naive and had genotype 1 infection. Most participants were white (83%), men (67%), and had the GT1a genotype (82%) and an IL28B non-CC genotype (67%). Only 9% of participants had cirrhosis, 10% in the 75-mg arm and 8% in the 150-mg arm. Age averaged about 55. At the end of treatment, 97.5% in the 75-mg arm and 94.2% in the 150-mg arm had an undetectable HCV load. Overall SVR12 (an undetectable load 12 weeks after treatment stopped) stood at 92.2% in the 75-mg group and 91.7% in the 150-mg group. The investigators counted 11 virologic failures, 6 in the 75-mg arm and 5 in the 150-mg arm. Failures included 2 on-treatment breakthroughs and 4 relapses before week 4 in the 75-mg group and 3 breakthroughs and 2 relapses in the 150-mg group. Everyone with virologic failure had genotype 1a. But SVR12s were 91% for 1a-infected people in both treatment arms. SVR12s were 100% for genotype 1b patients taking the lower dose of BMS-791325 and 94% in those taking the higher dose. Among people with cirrhosis, SVR12s were 100% in the 75-mg arm and 71% in the 150-mg arm, but the study included few cirrhotics. SVR12 varied little by study arm in people with an IL28B CC genotype or a non-CC genotype. While 2 people in the 75-mg group discontinued treatment, 6 in the 150-mg group discontinued. But only 1 person in each group discontinued because of adverse events. No one taking 75 mg of BMS-791325 stopped treatment for lack of efficacy, compared with 3 people taking 150 mg. Poor adherence explained 1 discontinuation in the 150-mg arm and none in the 75-mg arm. Serious adverse event rates were 1.3% with 75 mg of BMS-791325 and 2.3% with 150 mg. Respective discontinuations for adverse events were 1.3% and 1.2%. No one in the 75-mg arm and 1 in the 150-mg arm had a grade 3 or 4 adverse event. Headache was the most frequent adverse event, affecting about 25% of participants. Two phase 3 trials of the triple fixed-dose combination, UNITY 1 and UNITY 2, are fully enrolled (clinicaltrials.gov identifiers NCT01979939 and NCT01973049). UNITY 1 excludes people with cirrhosis and UNITY 2 includes people with compensated cirrhosis who may be randomized to add ribavirin to the triple pill. Almost everyone treated for 12 weeks with three direct-acting antiretrovirals (DAAs) for HCV genotype 1b infection had a sustained virologic response 12 weeks after treatment ended (SVR12), regardless of whether they added ribavirin to the three DAAs. Side effects proved more common and more serious among people randomized to ribavirin in this study of people without cirrhosis. With new DAAs for HCV infection proliferating, the race is on to identify effective, easy-to-take, and safe combinations that do not include either of the older toxic anti-HCV drugs, ribavirin and interferon. One candidate for this crown emerged in the PEARL III trial, which combined three DAAs made by the same company, AbbVie: (1) ABT-450, a ritonavir-boosted HCV protease inhibitor, (2) ABT-267, an NS5A inhibitor, and (3) ABT-333, a nonnucleoside polymerase inhibitor. The first two agents (and ritonavir) are combined in a once-daily fixed-dose formulation and, when combined with twice-daily ABT-333, are informally called 3D. PEARL III randomized 419 treatment-naïve, adults with genotype 1b HCV and without cirrhosis to 3D with weight-based ribavirin or ribavirin placebo. (Genotype 1b is the most prevalent HCV subgenotype worldwide.) The study excluded anyone with HBV infection, any HCV genotype other than 1b, and anyone with liver disease not caused by chronic HCV infec-

tion. Half of participants in the ribavirin arm (50.5%) and 41.1% in the no-ribavirin arm were men; 94% in each group were white. Age averaged 48.4 in the ribavirin group and 49.2 in the no-ribavirin group. The same proportion in each group, 21%, had the IL28B CC haplotype, which favors a good response to interferon/ribavirin. Pretreatment HCV RNA averaged 6.29 log10 IU/mL in the ribavirin group and 6.33 in the other arm. Twelve weeks after the 12-week treatment ended, 99.5% in the ribavirin group (209 of 210) and 99% in the no-ribavirin group (207 of 209) had a sustained virologic response (SVR12). The ribavirin-free regimen proved noninferior to the ribavirin-containing regimen (95% confidence interval for SVR12 -2.1% to 1.1%). Two people in the no-ribavirin group were lost to follow-up, one after treatment ended and one after achieving SVR for 4 weeks after treatment ended. PEARL III investigators recorded one on-treatment virologic failure in the ribavirin group and none in the no-ribavirin group. No one had a virologic relapse after completing 12 weeks of therapy. Virologic efficacy did not differ by gender, race (black versus nonblack), or IL28B genotype. Four people in each study arm had a serious adverse event. Researchers judged only one of these adverse events--arthritis in the no-ribavirin arm--as possibly related to study drug. Nineteen people randomized to ribavirin and none randomized to 3D alone had a hemoglobin drop to below 10 g/dL, a highly significant difference ($P < 0.001$). Everyone with low hemoglobin had a ribavirin dose reduction, and all achieved SVR12. Pruritus, nausea, insomnia, and cough also affected significantly more people randomized to ribavirin. Headache and fatigue affected about one quarter of participants in each study arm. No one dropped out of the trial because of adverse events or lab abnormalities.