Direct-acting antiviral regimens and HCV treatment failure and re-treatment in sub-Saharan Africa

Lancet Gastroenterol Hepatol 2022

Published Online
March 3, 2022
https://doi.org/10.1016/S2468-1253(21)00465-9

See Online/Articles
https://doi.org/10.1016/S2468-1253(21)00398-8 and
https://doi.org/10.1016/S2468-1253(21)00399-X

Today, most patients chronically infected with hepatitis C virus (HCV) can comfortably clear their infection after a 12-week course of direct-acting antivirals, which are easy to administer, well tolerated, and effective when administered as combination therapies.[1] However, treatment failure after the use of direct-acting antivirals for HCV infection, which can be recurrent, is an emerging worldwide problem and a threat to the global elimination of chronic HCV infection. Predictors of failure of direct-acting antiviral treatment include HCV genotypes, subtypes, and viral adaptations.[2] Treatment failure rates also vary with different combinations of antiviral drugs.

Data from sub-Saharan Africa on direct-acting antivirals and HCV treatment outcomes are scarce because of inadequate health-care delivery and low research capacity. The SHARED trial,[3] published in 2019, evaluated treatment of chronic HCV infection in treatment-naive patients in Rwanda with ledipasvir–sofosbuvir. In two single-arm follow-up studies (SHARED-3), published in *The Lancet Gastroenterology & Hepatology*, Neil Gupta and colleagues evaluated the safety and efficacy of sofosbuvir–velpatasvir-containing regimens to treat chronic HCV infection in patients in Rwanda: the first study investigated sofosbuvir–velpatasvir in treatment-naive patients,[4] while the second investigated sofosbuvir–velpatasvir–voxilaprevir in patients who previously had treatment failure with one or more courses of direct-acting antiviral drugs.[5] The patients in SHARED-3 were predominantly infected with HCV genotype 4 non-a/d subtypes, which are endemic to the region and frequently contain resistance associated-substitutions in NS5A.

In the SHARED trial,[3] 48 (16%) of 300 participants were infected with HCV genotype 4r. A sustained virological response 12 weeks after completion of treatment (SVR12) with sofosbuvir (400 mg) and ledipasvir (90 mg) was observed in 261 (87% [95% CI 83–91]) participants overall, 27 (56% [41–71]) of those infected with HCV genotype 4r, and 234 (93% [90–96]) of the 252 participants infected with genotype subtypes other than 4r. Overall, treatment failure in the SHARED cohort was higher than in comparable studies of sofosbuvir–ledipasvir treatment that included patients infected with HCV genotype 4 (overall SVR12s of 94%, 95%, and 99% among three small studies). The SHARED study also indicates that out of 100 patients in this region with HCV genotype 4r, we would expect that around 40 would have treatment failure, in contrast to around seven of 100 patients infected with other HCV genotypes. These findings do not support the use of sofosbuvir–ledipasvir as the initial therapy for HCV infection without genotype subtyping in this region.[6,7]

Following on from the SHARED trial, SHARED-3 investigated the suitability of alternative direct-acting antiviral regimens in treatment-naive patients[4] and in patients with a history of direct-acting antiviral treatment failure.[5] In the study of treatment-naive patients (n=61), among whom 11 (18%) were infected with genotype 4r, a 12-week course of sofosbuvir (400 mg) and velpatasvir (100 mg) was administered, and SVR12 was observed in 59 (97% [95% CI 89–99]) participants.[4] In the second part of the study, a 12-week course of sofosbuvir (400 mg), velpatasvir (100 mg), and voxilaprevir (100 mg) was given as salvage therapy to 40 participants (18 [45%] infected with genotype 4r) who had previously had treatment failure with sofosbuvir–ledipasvir or sofosbuvir–daclatasvir, or both. SVR12 was observed in 39 (98% [95% CI 87–100]) participants.[5] Among those infected with HCV genotype 4r, SVR12 was observed in ten (91%) treatment-naive participants[4] and 18 (100%) with previous treatment failure.[5]

Elsewhere, the POLARIS group of studies has reported outcomes for patients with HCV genotype 4 treated with sofosbuvir–velpatasavir or sofosbuvir–velpatasavir–voxilaprevir drug combinations. The POLARIS-2 study reported SVR12 in 56 (98%) of 57 treatment-naive patients infected with HCV genotype 4 following 12 weeks of sofosbuvir–velpatasvir treatment.[6] In the POLARIS-1 and POLARIS-4 studies of patients with HCV infection previously treated with either NS5A inhibitor-based or other direct-acting antiviral treatments, SVR12 following sofosbuvir–velpatasvir–voxilaprevir was observed in 20 (91%) of 22 participants and 19 (100%) of 19, respectively, among those infected with genotype 4.[7]

SHARED-3 indicates that sofosbuvir–velpatasvir is likely to be more effective than sofosbuvir–ledipasvir in preventing treatment failure in this population where genotype 4 non-a/d subtypes predominate.[8,9] However, according to the most recent treatment guidelines, sofosbuvir–velpatasvir–voxilaprevir would be the initial drug of choice for the treatment of patients with genotype 4r in this population.[1]

SHARED-3 provides preliminary data showing that patients who have had treatment failure with sofosbuvir–ledipasvir or sofosbuvir–daclatasvir, or both, can be successfully re-treated with sofosbuvir–velpatasvir–voxilaprevir. SHARED-3 also brings to the forefront the emerging problem of chronic HCV antiviral treatment failure in sub-Saharan Africa and the urgent need for improved access to regimens that can prevent treatment failure.[10] The use of drug regimens that prevent failure of treatment for HCV infection, active reporting of treatment failure cases, and pooling of these cases could provide a new opportunity to improve the delivery of care for people with HCV infection, access to medications, and research capacity in sub-Saharan Africa.

I declare no competing interests.

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