Further Information, Global Fund co-infection

The country-driven concept note development process for the next round of Global Fund financing is in full-swing. Countries will submit their concept notes during 2020. This is an important opportunity to include requests for support for hepatitis C (HCV) prevention, screening, diagnosis and treatment/cure among people living with HIV and for partners to support countries to do so.

Viral hepatitis is recognized as an important co-morbidity among people living with HIV. Higher rates of HCV, particularly among key populations, have been noted among people living with HIV than among the general population. Hepatitis C diagnosis and treatment among people living with HIV is recognized as eligible for support in current Global Fund policy and has been provided in the past to a small number of countries. Recent game-changing reductions in the cost of rapid diagnostic tests (RDTs), viral load tests and directly-acting antivirals (DAAs) have increased the feasibility of cost-effective approaches to micro-elimination of HCV among people living with HIV, and HIV/HCV co-infection programs have been and will continue to be catalytic for countries aiming to scale up viral hepatitis programs more broadly.

Countries that are interested in receiving HCV commodity support from the Global Fund for micro-eliminating HCV among their HIV/HCV co-infected population should work through the Country Coordinating Mechanism to allocate budget in the ***HIV Prioritized Funding Request*** submitted to Global Fund within one of the three 2020 windows (the first of which, March 23, is rapidly approaching). If the budget for HCV commodities does not fit within the *Prioritized Funding Request* allocation, it can be submitted as a ***Prioritized Above Allocation Request*** to be eligible for funding once additional resources become available on a rolling basis.

Quantification of HCV commodities required will depend on the country context, but commodity price assumptions should follow the below guidance based on pricing already achieved by countries:

- **Drugs**: Follow the latest GFATM HCV reference pricing of USD $79 per 12 week course of WHO Prequalified sofosbuvir/daclatasvir fixed dose combination and USD $93 per 12 week course of WHO Prequalified sofosbuvir/daclatasvir (ref pricing found at https://www.theglobalfund.org/media/7500/ppm_strategicmedicineshivreferencepricing_table_en.pdf)
- **Screening Kits**: USD $1 or less per WHO Prequalified rapid diagnostic kit
- **Viral Load**: The Global Fund is able to procure HCV viral load kits at **the same price as HIV viral load kits**. Pricing for HCV viral load kits will vary depending on what suppliers and platforms are being used by each country's HIV program.

Clinical rationale for prioritizing HCV cure in HCV/HIV co-infected population

Impact of HIV on Natural History of HCV Infection

Pre-existing HIV infection decreases the likelihood of spontaneous HCV clearance after exposure to the virus. Patients co-infected with HIV/HCV suffer from more liver-related morbidity and mortality, non-hepatic organ dysfunction, and overall mortality than HCV mono-infected patients. Research shows that HIV/HCV-coinfected populations progress to cirrhosis on average 12-16 years earlier than mono-infected patients and in some cases experience ultra-rapid progression in 2-8 years from primary HCV infection to cirrhosis. Co-infection with HIV results in earlier onset of Hepatocellular Carcinoma, with tumors that tend be more aggressive. Initiation on ART, improved immune status, and maintenance of an undetectable HIV

viral load has not been shown to slow the progression to cirrhosis and cancer, however, HCV treatment and cure have been shown to dramatically decrease the likelihood of these adverse outcomes to develop.

Impact of HCV on Natural History of HIV Infection

The impact of HCV infection on HIV outcomes is mixed. While some studies have shown HCV to have a negative impact on HIV outcomes, others have demonstrated it to be an independent risk factor for progression of HIV disease and AIDS. Evidence supporting a detrimental effect of HCV on HIV disease demonstrate: 1) Individuals co-infected with HIV and HCV have a higher risk of HIV- and AIDS-related mortality than HIV mono-infected patients; 2) increased mortality has been observed across various HIV-risk groups e.g. PWID, MSM; 3) co-infection is associated with higher incidence of AIDS-defining illnesses and increased generalized immune activation; 4) the presence of HCV infection can lead to lower CD4 gains and higher risk of immunologic failure; and 5) co-infected patients have an increased risk of hepatotoxicity from ART. Furthermore, multiple studies, including a Swiss cohort of 3,111 ART naïve patients who initiated ART, have shown HCV co-infection to be an independent risk factor for progression to a new AIDS event or death.

Hepatitis-related deaths in Persons living with HIV (PLHIV)

Despite mixed evidence of HCV impact on HIV progression, HBV and HCV infection are a leading cause of mortality among PLHIV. Several large cohort studies in Europe have demonstrated that persons with HIV-HCV co-infection have higher rates of liver-related death compared to persons with HCV mono-infection. In the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort study, 14.5% of PLHIV deaths resulted from liver-related causes and HCV infection was a predictor of liver-related death. In follow-up analysis, the percentage of liver-related deaths has decreased over time but remained the third leading cause of death (13%).

References

Impact of HIV on Natural History of HCV Infection:

Lower rates of spontaneous clearance after acute exposure; mono-infected have ~20-25% clearance, HIV-HCV co-infected have ~5-15% clearance

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Increased mortality compared to HCV mono-infected

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Accelerated liver fibrosis and cirrhosis

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Accelerated Hepatocellular Carcinoma and aggressive tumors

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Impact of HCV on Natural History of HIV Infection:

Individuals co-infected with HIV and HCV have a higher risk of HIV- and AIDS-related mortality than HIV mono-infected patients

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- *Daar ES, et al. Relation between HIV-1 and hepatitis C viral load in patients with hemophilia. J Acquir Immune Defic Syndr. 2001;26(5):466.*
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Increased mortality has been observed across various HIV-risk groups e.g. PWID, MSM

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Co-infection is associated with higher incidence of AIDS-defining illnesses and increased generalized immune activation

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Presence of HCV infection can lead to lower CD4 gains and increased hepatotoxicity risk, upon initiation of ART

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HCV co-infection has been demonstrated to be an independent risk factor for progression to a new AIDS event or death

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Hepatitis-related deaths in Persons living with HIV (PLWHIV):

HBV and HCV are a leading cause of mortality among PLHIV

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PLHIV deaths resulted from liver causes and HCV infection was a predictor of liver-related death. In follow-up analysis, the percentage of liver-related deaths is the third leading cause of death.

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