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# Latent tuberculosis infection screening in HCV patients: The necessity and guidelines for Pakistan

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Dear editor,

World Health Organization (WHO) deals tuberculosis (TB) on priority basis in developing countries, with main focus on surveillance and treatment. As these countries have poor health care system, low economic status and poor sanitary set up, TB has high incidence and mortality rates in these communities[1]. TB is an air born infectious disease; it is caused by a bacterium called *Mycobacterium tuberculosis* (*M. tuberculosis*). The infection rate of *M. tuberculosis* is higher in certain groups as compared with general population. The high risk groups for *M. tuberculosis* infection include HIV/AIDS and hepatitis C Virus (HCV) positive patients. Other vulnerable groups are patients under treatment for rheumatoid arthritis, inflammatory bowel disease, kidney disease, diabetes and individuals with organ transplant [2]. Recently, it has been highlighted that there is higher TB incidence in patients treated for HCV infection [3]. In this report, analysis was done on TB incidence during interferon-based treatment for hepatitis C. The data showed that most of the HCV positive patients (89%) were treated with double therapy, *i.e.* interferon (pegylated or not) plus ribavirin. Due to *M. tuberculosis* coinfection HCV treatment was discontinued in 67% of cases. Among patients who completed antiviral therapy; sustained virological response (SVR) was attained in 33 %, 28% patients were relapsed and other were non-responders. Another important aspect of the analysis was that in majority of HCV positive patients (83% of cases) sign and symptoms of TB appeared during third and fourth trimesters of interferon treatment. In some cases interferon based antiviral treatment patients showed TB symptoms after completion of therapy (three to six months after therapy). The mechanism of TB reactivation after HCV antiviral therapy can briefly be explained as a result of down regulation of the early immune response against *M. tuberculosis* during interferon therapy. Type 1 immune response restrains *M. tuberculosis*. It is characterized by production of cytokines like lL-12, IFN-γ and TNF-α. The anti-HCV interferon therapy suppresses this type 1 immunity and can lead to *M. tuberculosis* reactivation. *M. tuberculosis* reactivation can also partially be explained by the role of leukopenia, neutropenia, a lowering on CD4 positive T lymphocyte population and abnormalities on chemotaxis and phagocytic functions of macrophages[4]. In the light of above observation, it is highly recommended to establish protocols in clinics for this problem. Pakistan is a resource constrains country with low per capita income and poor sanitary system. It ranked second in the world in term of HCV burden with more than 10 million infections[5,6]. Epidemiological data of HCV prevalence from last seven years (2010–2016) is reviewed and summarized in Figure 1. The data from 52 studies of HCV prevalence in general population, healthy blood donors and various high risk groups showed very high prevalence across the Pakistan. Its burden is expected to increase in coming decades mainly because of unsafe and substandard of syringe use, medical procedures, dental procedures, blood transfusions, and barbers practice. All these issues arise due to unawareness about transmission routes of infections in general and high risk population groups[7]. Interferon based antiviral therapy is genotype dependent so the data analysis of HCV sero-prevalent genotyping is carried out (Figure 2). The data review showed that previous and current antiviral treatment in Pakistan is interferon based and in current scenario it might remain the choice in coming years[8] mainly because of lower cost and higher efficacy against major prevalent genotype in the country *i.e.* genotype 3. As interferon based treatment could leads to TB reactivation, the higher burden of TB in Pakistan might be explained by de Oliveira Uehara *et al*.[3]. In 2009, Pakistan ranks 8th in the world in term of TB

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burden and share about 44% of tuberculosis burden in the Eastern Mediterranean region[9]. In 2012, due to increase in TB burden Pakistan ranked 6th in the world[10] and according to WHO 2016 report, Pakistan ranks 5th among TB high-burden countries in the world. According to this report, it is 61% of the TB burden in Eastern Mediterranean region and approximately 420 000 new TB cases are emerging every year[11]. These facts and figures reflect the higher incidence of TB during HCV treatment with interferon regimen. It could be concluded that a large number of TB incidence and reactivation in Pakistan is might be linked to immune suppressive role of antiviral interferon therapy. Another drawback due to reactivation of TB is the HCV patients will not achieved sustained virological response (SVR), which will affect the HCV future burden in the country. Lower SVR will have adverse effects on HCV patients and their families, it will result in loss of resources in already resource constrained country.

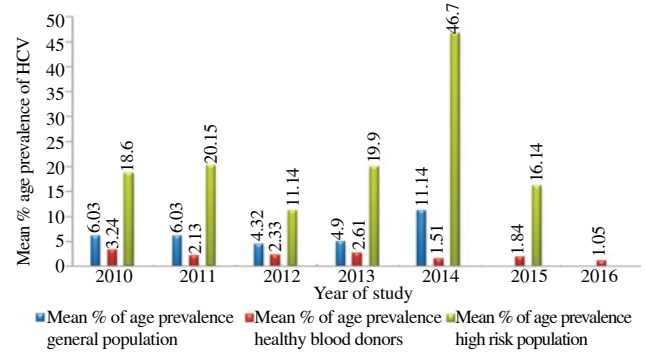


**Figure 1.** Hepatitis C virus seroprevalence in Pakistan (2010–2016).

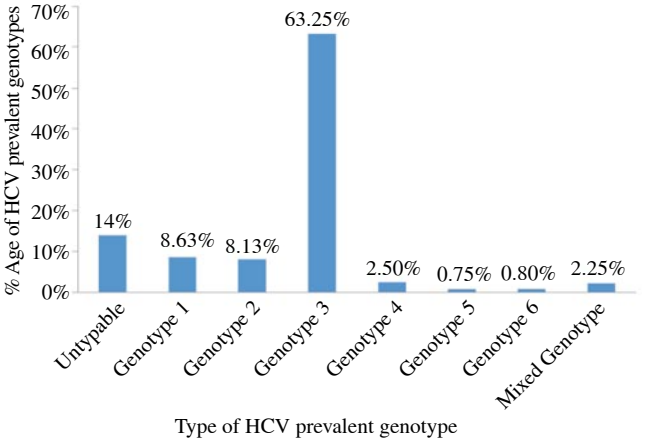


**Figure 2.** HCV prevalent genotypes in Pakistan (2010–2016).

On the basis of above discussions, following recommendations are proposed which should be implemented and followed by health care sector of Pakistan:

• Latent tuberculosis infection (LTBI) screening by tuberculin skin test/or by interferon gamma releasing assays, before starting IFN-based antiviral treatment.

• High risk groups for TB reactivation should be screened before anti-viral treatment.

• For LTBI positive hepatitis C patients, direct-acting antivirals (DAA) should be considered to avoid TB reactivation.

• HCV positive patients treated with DAA should be screened for LTBI and followed for TB reactivation to check the effect of DAA on TB reactivation.

• Massive educational campaigns regarding TB reactivation by interferon based antiviral treatment should be governed for health care workers.

• Government, researchers, educationalists, community workers should take steps for community education in general population and high risk groups regarding LTBI screening before immune-suppressive treatment.

## Conflict of interest statement

We declare that we have no conflict of interest.

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