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MINI REVIEW

Does Dolutegravir-based Treatment in HIV-infected Diabetic Individuals require more Intensive Cardiovascular Health Monitoring: A Point of Concern for Developing Nations

Dipankar Pal*

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Abstract

We are all aware that obesity is a growing health problem globally. An estimated 600 million adults are affected with some form of obesity-related metabolic complications worldwide. It increases cardiovascular disease, diabetes mellitus, chronic kidney disease, nonalcoholic fatty liver disease, and cancer in the long run. Human immunodeficiency virus (HIV) infection is a common occurrence throughout the World. Developed countries can access early diagnosis, standardized treatment protocols, and close monitoring. It not only prevents incidences of opportunistic infections but also takes care of non-infective complications. On the contrary, lack of education, awareness, and access to good healthcare facilities are often responsible for delayed diagnosis and advanced disease at presentation. Even those who are initiated on therapy also have persistent modifiable risk factors for cardiovascular events. The Importance of regular exercise, a healthy diet, and tight control of blood sugar, hypertension, and dyslipidemia are often under-practiced and must be stressed.

Key Words: *Dolutegravir; Weight gain; Deranged glucose metabolism; Cardiovascular monitoring*

Discussion

Post-therapy initiation weight gain is a good metric of improvement in HIV-infected individuals who are underweight initially [1-3]. However, weight gain may increase the risk of cardiovascular and metabolic diseases -in those with baseline obesity [4-6]. Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), has been included in the standard triple-drug combination regimen in developing countries like India for several years. It has excellent efficacy and tolerability. It achieves rapid viral suppression and good CD4 cell recovery when combined with tenofovir and lamivudine as shown in various trials. It has a higher genetic barrier for the development of resistance in comparison to non-nucleoside reverse transcriptase inhibitors (NNRTI) like nevirapine and efavirenz. Hence, the majority of national AIDS control programs have replaced NNRTIs with dolutegravir [7-10].

All INSTIs are generally well tolerated. However, they are often associated with more weight gain than other agents. Sax PE

Infectious Disease Consultant, Department of Infectious Diseases, Christian Medical College, Vellore, India

Corresponding author: Dipankar Pal, MD, DM, Infectious Disease Consultant, Department of Infectious Diseases, Christian Medical College, Vellore, India, E-mail: dipankarpal.2009@gmail.com

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et al., found in their analysis of 8 randomized controlled trials that multiple baseline demographic factors are associated with weight gain while on INSTI therapy [11]. Important determinants were lower CD4 cell count, higher HIV-1 RNA, no injection drug abuse, female sex, and black race. In developing countries, many patients are still being diagnosed with advanced HIV infection with very low CD4 cell count. Mostly, they are infected with HIV-1, and females are the most neglected ones, as usual. This may amplify the metabolic problems in the underprivileged section. When compared, INSTI use was associated with more weight gain than with protease inhibitors or NNRTIs. DTG was associated with more weight gain among all INSTIs. Other agents like bictegravir performed better than DTG. This study saw a weight gain of up to 3.5 kg at 96 weeks of follow-up. However, the mechanism for this weight gain was not entirely known.

Norwood J et al. in their retrospective observational cohort study, have shown that patients who switched to an INSTI-based regimen gained a median of 2.9 kg of body weight at 18 months compared with 0.9 kg among those who continued on efavirenz-based therapy and 0.7 kg among protease inhibitor recipients [12].

It is conclusively proven from the above discussion that DTG usage is associated with significant weight gain among HIV-infected people. HIV itself is associated with more cardiovascular disease and is an age-old concern [13]. As India is the 'diabetes capital' of the World, coupled with a lack of access to antidiabetic medications for a poverty-stricken population, poor knowledge about the benefits of optimum diabetes control may further lead to increased cardiovascular diseases in coming years [14]. As we are using DTG as our 1st line ART regimen endorsed by the various National programs, a large number of HIV-infected population cohorts are being exposed to it. Whether the cumulative effects of DTG exposure, inadequate diabetic control, lack of healthy lifestyles, and poor access to diabetic medications will lead this group of patients to have more cardiovascular deaths is a matter of concern. A cross-sectional study in Tanzania was done on 223 patients in 2020, and it showed that the only factor associated with metabolic syndrome was increased body mass index among the participants [15]. The African Cohort Study (AFRICOS) prospectively followed adults with and without HIV in Kenya, Uganda, Tanzania, and Nigeria. Those on TLD gained an average of 0.68 kg (95% CI: 0.32-1.04) more than those on other regimens. It was found after adjusting the result for the duration on ART, sex, age, study country, and CD4 nadir [16].

In addition, insulin resistance might be worsened by immune activation and chronic inflammation due to HIV infection. Deranged glucose metabolism with INSTIs use is found in multiple studies like SAILING, SPRING-2, SINGLE, and VIKING-3 [17-20]. These studies reported moderate (plasma glucose, 126-250 mg/dl) and severe hyperglycemia (plasma glucose, >250 mg/dl) in 6-9% and 1-2%, respectively, post INSTIs therapy. Severe hyperglycemia with or without ketoacidosis or hyperosmolar coma is also reported in these studies. INSTIs prevent HIV from getting incorporated into host cell DNA by chelating magnesium ions. Magnesium ion is required for the post-receptor effect of insulin and thus INSTIs are responsible for deranged glucose metabolism. Analysis of the above studies showed the lipid-neutral effect of INSTIs on 48 weeks of follow-up [21]. NEAT-002 is a randomized controlled trial comparing protease inhibitors with DTG. A post-hoc analysis at 96 weeks showed that switching to DTG did not negatively impact the incidence of hypertension or blood pressure changes relative to continuing protease inhibitors [22].

Conclusion

Randomized controlled trials in this aspect are needed to determine the direct effect of DTG on cardiovascular events. Increased awareness among HIV-infected people regarding tight blood sugar control, maintaining an optimum body mass index, and counseling about a healthier lifestyle through a robust antiretroviral therapy (ART) center network may prove beneficial in developing nations.

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