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Perspective

HIV-2: still off the radar for India's 90-90-90 targets

Human immunodeficiency virus (HIV)-2, a kin of HIV-1, still considered to be confined to the African subcontinent, has spread its roots across the globe in countries such as Europe[1], America[2] and India[3]. The test and treat strategy being implemented globally for HIV-1 has shown reductions in the epidemic-limiting AIDS-related deaths and new infections[4]. However, there seems to be no road map in the case of HIV-2 for achieving the target of 'ending AIDS by 2030'. The sole reason behind HIV-2 being neglected globally is that none of the global agencies (WHO and UNAIDS) have a formal surveillance system for HIV-2, which makes it difficult to know the updated epidemiology and geographical distribution of the infection which form the basis for interventions and research to tackle it[4,5]. Also, lack of surveillance reports from some areas where although the infection exists and qualifies the definition of a neglected tropical disease results in inaccurate prevalence[6]. In India, National agencies such as NACO (National AIDS Control Organisation) have a formal surveillance system in place for HIV-2 through integrated counselling and testing centres, regional laboratories and an apex laboratory network across the country that accounts for total HIV-2 cases detected annually[7,8], of which HIV-1+2 dual infection cases are referred to the apex laboratory for molecular testing, though counts for both mono as well as dual infections are unpublished[9]. So far, the highest number of HIV-2 cases reported from India are compared to the rest of Asia[10]. Sparse data are available from few parts of the country with potentially high HIV-2 cases[3,10,11].

The HIV-2 90-90-90 road map for India

In India, to achieve the first 90 of the UNAIDS ambitious 90-90-90 treatment target to end AIDS epidemic, 90 per cent of people living with HIV-2 should know their HIV status. Technological advances have introduced modern epidemiological and laboratory methods for differential diagnosis of HIV-1 and serially with 2nd, 3rd and 4th generation serological tests; however, scope for technological advancements in these assays for rapid, point-of-care antigen (Ag)/antibody (Ab) tests capable of differentiating HIV-1 and -2 individually and/or in combination exists. The Indian national programme employs 2nd and 3rd generation differential diagnosis assays which on occasion are complimented with nucleic acid test (NAT)[8,11]. But this is also a limitation since there is no commercial FDA-approved NAT for HIV-2[11,12]. This makes NAT-based confirmation of the HIV-2 infection in case of dual infection limited and centralized which is practiced at national apex laboratories and some regional centres and not at the point-of-care with in-house assays. To catch up with the 90-90-90 timelines, it is essential to close this diagnostic gap for confirming HIV-2 infection with rapid and affordable point-of-care assays.

The genesis of the HIV-1 test and treat strategy is from global studies and clinical trials that support early antiretroviral therapy (ART) initiation for reducing HIV-1 transmission[13,14] and sustained ART for achieving viral suppression and minimizing drug resistance. Per contra, there exists a lack of profusion of basic research and clinical experience that could serve as guidance in case of HIV-2[15]. The existing NACO guidelines for HIV-2 are based on sporadically reported individual case studies, a few retrospective cohorts which are unable to create a strong base for initiating the ART regimen[7]. These need to be refurbished with results of the trials published in 2018 that give evidence-based recommendations for preferred first-line and second-line regimens which clearly outline criteria for ART initiation after treatment failure for HIV-2 alone and HIV-1+2 dual infection[16,17]. These also highlight the use of integrase inhibitor (raltegravir)–containing first-line regimen as a safe option[16]. Like many developing countries, India is also attempting free roll out of ART under the test and treat strategy to achieve the second 90 of the 90-90-90 treatment

target, which aimed that, 90 per cent of all people with diagnosed HIV infection will receive sustained ART[18,19]. However, HIV-2 features nowhere in these strategic plans[11] . The finite choice of antiretroviral drugs [NRTIs, protease, integrase and entry inhibitors (PI, II and EI)]; programmatic limitations of using PI, II and EI; unavailability of active (*i*) triplet single-tablet II containing first-line raltegravir-emtricitabine-tenofovir combination[7,15,16], (*ii*) quadruple single-tablet regimens containing four HIV-2-active retrovirals, *viz*. elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate[17]; non-routine screening strategies for hypersensitivity syndrome for abacavir usage[18,20]; insufficient data to justify the use of PI and II as the preferred first-line for HIV-2 given their higher cost, *etc.* make the roll out of the HIV-2 ART challenging in developing countries like India[15-20]. In addition, the Indian ART programme needs to be strengthened with essential monitoring assessments that include routine HIV-2 viral load measurements as employed for HIV-1[21]. In case of HIV-1+2 dual infections, there is lack of information available on choosing the optimal antiretroviral regimen that is active against both the viruses[22]. Also for this, the monitoring of such patients for virological failures requires inclusion in the mainstream viral load and drug resistance testing for both the viruses. Furthermore, as mentioned earlier unavailability of commercial FDA-approved HIV-2 viral load tests serves as the limitation for programmatic prognostic assessments.

The third 90 of the UNAIDS ambitious 90-90-90 treatment target, aimed that 90 per cent of all the people receiving ART will have viral suppression (undectable/ untransmittable), however, the same cannot be mapped without HIV-2 viral load tests[23,24]. Hence, it is essential to develop decentralized capacity not only for HIV-2 NAT but also for HIV-2 viral load tests (DNA or RNA based) at point-of-care for efficient monitoring of virological failure during the roll out of the HIV ART programme[24]. Rather, the second and the third 90-90-90 targets go hand in hand as HIV-2 viral load is an early virological indicator for drug resistance and both of these are indespensible in sustained therapy monitoring, leading to viral suppression. Implementation of these in developing countries is challenging as specialized facilities and centres are needed to meet and aid the diagnosis and prognosis arms[25,26]. These tests are further complexed with high equipment costs and high cost per test[19,23]. It is essential that all these factors need to be addressed before rolling out efficient antiretroviral programmes. Strategies such as 'network viral load' should be adopted to have a more precise metrics of the infection in high-risk pockets[27].

Overall, although the patients with HIV-2 infection form a small subset as compared to HIV-1–infected patients, they deserve, uniform access to treatment and clinical management in spite of the posed challenges. Many strategies currently being used to curtail HIV-1 are likely to be effective against HIV-2 as well and may assist in developing a clear road map. However, this does not disregard the unique challenges that HIV-2 infection presents to individual patients, caregivers, researchers and national programme activities[28]. These aforesaid perspectives need prompt attention at individual and programmatic level to map HIV-2 in and indicate the need of concentrated and multifocal efforts for curtailing HIV-2 along with HIV-1 to achieve the 90-90-90 global targets[10,29].

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