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Commentary

A push for 90-90-90: Initial treatment with INSTI-based regimens against HIV-1 infection

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In recent years, the global scenario of HIV infection has dramatically changed with the widespread implementation of antiretroviral treatment (ART) and the aim to reach the goals of the UNAIDS initiative "90-90-90: Treatment for all" (www.unaids.org/en/resources/909090) by 2030. Furthermore, ground-breaking scientific evidence has revolutionized the life of people living with HIV/AIDS (PLWH). Undetectable equals untransmittable (U = U) is one of the most important messages since the rise of HIV epidemic with the power to reduce the stigma related to infectiveness [1]. Among the potential strategies to be implemented to end HIV epidemics, treatment as prevention is the one with the strong scientific evidence [2].

In their work Zhu J *et al* have formalized a model assessing the potential impact of integrase strand-transfer inhibitor (INSTI)-containing regimens in reducing onward HIV transmissions in British Columbia [3]. By applying two previously described models of HIV transmission [4,5], which are based on HIV-RNA viral load and the natural history of HIV infection (early *vs* chronic *vs* late), the authors demonstrated how the use of INSTI-based regimens in naïve patients could potentially reduce the risk of HIV transmission when compared to non INSTI-based regimens in their cohort. In particular, a HIV transmission risk reduction of 25%, according to the model by Fraser C *et al*, has been estimated for gay, bisexual and other men who have sex with men (gbMSM) starting an INSTI-based regimen with a viral load $\geq 5 \log_{10}$ copies/mL irrespectively of HIV stage [5]. Authors concluded that INSTI-based regimens have the potential to avert onward HIV transmission by achieving a fast virologic suppression, in particular among gbMSM with pre-treatment high viral load.

Although these data are sound, some potential pitfalls should be acknowledged to correctly interpret the findings reported by Zhu J et al. Firstly, the time span covered by the study is between 2011 and 2016 and only 376/1459 (25.8%) of the patients in the cohort started the treatment with and INSTI-based regimen. These findings are partially overcome by the widespread use of INSTIs in recent years due to the high efficacy, improved safety profile and, more recently, dolutegravir-based antiretroviral drug regimens implementation strategies in resource limited setting. Secondly, 46% of the patients started antiretroviral treatment with <350 CD4 cells/mm^3, reflecting the prescription recommendations followed until 2015, when the INSIGHT START trial demonstrated the incontrovertible beneficial effects of starting ART irrespectively of the CD4 cells count [6]. In other words, the findings of the authors should be considered as confirmatory and add a strong scientific evidence to a change in the prescribing behaviour occurring in everyday clinical practice. Moreover, the study relies on the assumption that there are no changes in the behaviours of a newly infected PLWH. However, it could not be excluded that changes in the sexual behaviours after the diagnosis - due to extensive counselling and a novel risk perception - could impact on the risk of HIV transmission [7].

The authors focus their attention on a high-risk gbMSM population who show the highest number of previous condomless sexual intercourses. In this population, the use of INSTIs is advisable not only to reduce HIV risk by dropping the time of HIV-RNA detectability (defined as HIV-RNA >200 cp/mL), but also by reducing the risk of potential drug–drug interaction with chem-sex compounds [8]. The burden of drugs resistance to antiretrovirals is still the main cause of virologic failure, at least in developed countries. The impact of INSTI drug resistance within the first-line treatment is still very limited [9], thus this pharmacological class is potentially useful in all HIV-1-infected individuals who start their first ART.

When we think about the potential window of HIV transmission opportunities after the engagement in care of PLWH, it's important to consider the timespan between HIV diagnosis and ART initiation. In fact, the potential advantage of HIV-RNA rapid reduction obtained with INSTI-based regimens should be considered additive to the "same day strategy" which is potentially practicable with high genetic barrier INSTIs, such as dolutegravir and bictegravir. The "same day strategy" has been demonstrated to increase the linkage to care of PLWH by reducing the stigma and the fear related to the infectiveness [10].

Ending HIV epidemic is an ambitious goal and no single intervention by itself is able to interrupt the transmission chain. Conversely, a multilevel intervention strategy relying on prevention strategies (*i.e.* U = U and pre-exposure prophylaxis implementation) combined with

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universal ART coverage with highly effective, well tolerated new drugs, such as INSTIs in resource limited setting, would be able to close the gap within 2030, making 90-90-90 not just a dream but a matter of fact.

Declaration of Competing Interest

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