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Editorial

HIV prevention & treatment - Reasons to rejoice & remain vigilant

Considerable efforts in HIV prevention and treatment have been deployed over the past decade by national health authorities, non-governmental and community-based organizations, with long-term commitment by defining coherent and adaptive policy, accelerating the implementation of efficient strategies, and allocating adequate funding. Despite undeniable gaps in HIV prevention and in access to care and treatment of key populations[1], an overall decrease of HIV prevalence, mortality and morbidity of HIV-infected individuals under antiretroviral therapy (ART) is observed in several countries. HIV infection has become a manageable chronic condition.

Current situation of the HIV epidemic in Asia

While the vast majority of HIV infections continue to occur in Sub-Saharan Africa, a recent review of the HIV epidemic in Asia indicates that there are 4.8 million people living with HIV. Low national prevalence masks higher HIV prevalence and incidence rates in key populations with mixed pictures between and within countries[2]. The number of AIDS-related deaths in Asia fell by 37 per cent between 2005 and 2013[2].

New HIV infections are concentrated among key populations at higher risk, more difficult to reach due to stigma and legal barriers. These key populations include people who inject drugs (PWID), female sex workers (FSW), men who have sex with men (MSM) and transgender (TG) women. In low- and middle-income countries, the burden of HIV infection was disproportionately high among FSW in Asia and the Pacific, with a 29-fold increase in odds of living with HIV compared with women of reproductive age[3].

Estimates based on country information indicate that the regional population of MSM and TG who are at risk of HIV infection ranges from 10.5-27 million[1]. TG women are 50 times more likely to acquire HIV than adult males or females of reproductive age. For example, 18 per cent of surveyed male sex workers in Indonesia and Thailand tested HIV-positive, 31 per cent of TG sex workers in Jakarta, and 19 per cent in Maharashtra[1].

India continues to portray a concentrated epidemic. The HIV prevalence among high-risk groups, *i.e.* FSW, PWID, MSM and TG is about 20 times higher than the general population[2]. A recent study conducted in 2013 among PWID from 15 cities showed that estimated HIV prevalence and incidence were 18.1 and 2.9 per cent, respectively[4]. Sex work continues to be the most important source of HIV infection in India. The estimated HIV prevalence among MSM ranges between 7 and 16.5 per cent[5]. HIV prevalence was characterized among MSM in eight cities from Tamil Nadu where 34 per cent were married and 40 per cent self-identified as homosexual. HIV prevalence was nine per cent, higher among married men (14%)[6]. A recent study conducted among MSM across India confirms a relatively high HIV prevalence of seven per cent and a low HIV incidence of 0.87 per cent (0-2.2%)[7]. MSM who reported injection drug use were 6.7 times more likely to be HIV-infected. Heterosexual anal sex was reported by 11.9 per cent FSW in four high prevalence States in India[8]. A meta-analysis of studies from developed countries has shown that the probability of HIV transmission is higher per act of receptive anal sex (1.7%) as compared to peno-vaginal sex (0.8%)[9]. Individuals with acute HIV infection have 8- to 26-fold greater risk for transmitting HIV compared to those with chronic infection because of their high viral load[10] while they may remain undiagnosed by routine

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antibody tests. Phylogenetic clustering of new HIV infections in MSM supports acute HIV infection as one of the main drivers of ongoing HIV transmission in MSM in rising and ongoing HIV epidemics.

Achievements and reasons to rejoice

Political willingness, long-term commitment, clearly defined multi-sectorial policy, combined and scaled-up strategies, and adequate and sustained funding are key elements of success. Improved approaches to the prevention of mother-to-child transmission have averted the deaths of more than one million children worldwide. The rate of male acquisition of HIV can be diminished by two thirds through voluntary medical male circumcision[11].

The scale-up of ART averted 5.4 million deaths in low- and middle-income countries worldwide between 1995 and 2012. Given the limitations of ART and recent advances in our understanding of HIV persistence with current treatment regimens, there is a growing recognition, although a remote dream, that a functional cure for HIV infection is both needed and feasible[12]. Several clinical trials are ongoing with various drugs and broadly neutralizing monoclonal antibodies administered during the early acute HIV infection phase to study whether HIV viral load would remain undetectable after treatment interruption.

Clinical trials of oral PrEP (pre-exposure prophylaxis) for HIV-negative individuals conducted in Thailand showed a reduction in HIV acquisition in MSM[13], and in PWID[14]. The US FDA (Food and Drug Administration) approved daily oral Truvada for PrEP in 2012 and WHO and CDC recommended PrEP for certain populations. The PROUD and on-demand 'Ipergay' PrEP studies showed a relative reduction of 86 per cent in HIV incidence among MSM[15,16]. Long-acting injectable PrEP may have the preference of target populations and circumvent the issue of adherence but the supply of the drug would need to match the increasing demand to ensure success of this new biomedical prevention modality. Key for optimum coverage, PrEP costs should be covered by the national health programmes where PrEP is now recommended.

Treating infected persons with combination ART dramatically reduces their likelihood of transmitting HIV to an uninfected partner. The efficacy of this strategy known as 'Treatment as Prevention (TasP)' is illustrated by several studies. HPTN 052 trial[17,18] demonstrated that early ART reduced the risk of heterosexual HIV transmission by 96 per cent in discordant couples. In India, early ART was cost-effective over a 5-year period and very cost-effective over a lifetime[19]. A recent modelling study in India suggested that in the presence of existing condom-based interventions, existing ART programmes could avert 11-28 per cent of remaining HIV infections in FSW between 2014 and 2024[20].

Significant advances have been achieved in HIV vaccine development. A community-based Phase III trial (RV144) provided the first evidence that an HIV-1 vaccine might prevent HIV infection in humans[21]. The vaccine regimen conferred a 31.2 per cent efficacy after 42 months of follow up. In a post-hoc analysis, vaccine efficacy was significantly higher (60%) at 12 months post-vaccination, suggesting an early, but non-durable, vaccine effect. The RV144 immune correlates of risk analysis showed that IgG antibodies to the V1V2 region of gp120 correlated with decreased risk of infection while IgA antibodies to Env were directly associated with infection risk. These correlates were supported by a "sieve" analysis of breakthrough viruses suggesting that genetic mutations away from V2 sequences found in the vaccine were associated with altered efficacy[22]. Whether various envelope immunogens eliciting V2 antibodies are functionally strain-specific, region-specific or universal in a cross-clade manner and universal correlates of risk in populations with various modes of transmission remain to be demonstrated in future efficacy trials. Other vaccine approaches for a globally effective vaccine including immunogens derived from conserved or mosaics sequences expressed by various vectors are being developed[23]. Our current understanding of the immune correlates of protection suggests that no specific vaccine approach should be privileged over the other and that all reasonable vaccine approaches deserve to be pursued.

Reasons to remain vigilant

The overall ART coverage of 30 per cent in Asia and the Pacific remains far insufficient including for prevention of mother-to-child transmission programmes. One could argue that the reduction in HIV incidence has occurred in several countries without a vaccine and with still very limited use of PrEP and TasP[24]. Moreover, scale-up of PrEP and TasP may significantly revert the HIV epidemic in key populations in a near future. This raises the question of whether a vaccine is necessary to end the pandemic. This question must be put in perspective and appreciate the differences in the epidemic and socio-economic

patterns between Africa and Asia and the substantial barriers to non-vaccine HIV prevention hindering public health efforts.

The most challenging of these relate to human behaviour. Prevention of HIV infection usually requires people to continually make positive health choices. Social context affects individual behaviour and often negatively influences the effectiveness of biomedical preventive interventions. Even if HIV prevention efforts were optimally implemented to achieve a new infection rate of near zero, 'disinhibition' could revert this success. Cultural factors have probably slowed adoption of male circumcision - less than one quarter of the targeted 20 million African men have undergone the procedure[11]. Legal factors also slow progress since homosexuality, prostitution and drug use remain illegal in several countries. TasP is similarly complex, given that only a fraction of HIV-infected people benefits of the care continuum to achieve an undetectable viral load with ART. TasP would have a maximum efficiency if ART were provided during the early HIV infection phase, which remains a challenge in most countries.

Health officials and funders may be tempted by impressive reductions in HIV infections by decreasing funding and attention paid to control programmes, with the negative consequence of resurgence of the HIV epidemic, particularly in the absence of a sustainable solution like a vaccine. Therefore, although it might be possible to control and even end the HIV-AIDS pandemic using existing interventions, in order to reach this goal more quickly and to sustain the success, a safe and at least moderately effective HIV vaccine may remain essential. However, the ultimate choice of combined prevention interventions should remain adaptive to the evolution of the epidemic and to their cost-benefit analysis.

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