Hot News

Sexually Transmitted Infections in Men having Sex with Men - Rising Numbers and Wider Etiologies

Classical sexually transmitted infections (STI), namely, syphilis, gonorrhea, trichomonas, and chlamydia, are on the rise worldwide. Sporadic cases and outbreaks mostly in men having sex with men (MSM) are responsible for the current STI rebound. The loss of fear to acquire HIV, given the success of antiretroviral therapy as prevention, is the major determinant for increased sexual risk behaviors. The advent of chemsex and internet has further fueled the opportunities for STI spreading (*Soriano, AIDS Rev.* 2018;20:187-204).

Although MSM may act as the epicenter of the ongoing global STI rebound, a subset of MSM is bisexual and might spread STI to women and subsequently to the heterosexually active population. In this way, focusing actions primarily on MSM would be the most cost-effective intervention. Three major actions can be considered: first, vaccination for all potentially sexually transmitted agents for which there is a vaccine; second, earlier diagnosis and STI treatment by promoting frequent periodic STI screening for halting further transmissions; and third, providing specific education, counseling, and psychological support when needed.

Although there is no vaccine for syphilis, gonorrhea, trichomonas, or chlamydia - the four classical major STI - vaccines are available for others, including hepatitis B or papillomavirus. During the last couple of years, outbreaks of sexually transmitted hepatitis A (*Puoti et al., Liver Int.* 2018;38:581-4) and meningococcus (*Harrison et al., Sex Transm Infect.* 2017;93:445-51; *Nanduri et al., MMWR.* 2016;65:939-40) have highlighted the need for keeping clinical suspicion on these new agents among MSM, for which there are effective vaccines.

The need for considering new STI agents must be emphasized in the light of anogenital and orogenital sexual relationships. The nasopharynx of 3% of adults is asymptomatically colonized by *Neisseria meningitidis.* One serotype C strain seems to be particularly pathogenic and transmissible (*Kahler, Trends Microbiol.* 2017;25:510-2); being responsible for cases of urethritis, proctitis, and disseminated disease, including sepsis and meningitis, among MSM (*Taha et al., PLoS One. 2016;11:e0154047*) and heterosexual promiscuous men (*Bazan et al., Clin Infect Dis.* 2017;65:92-9). Orogenital relationships are behind these outbreaks.

Hepatitis A virus (HAV) has been generally considered an enterically transmitted agent. Accordingly, the orofecal route accounts for early age exposure to HAV through contaminated water and foods in developing countries with poor sociosanitary conditions. In contrast, in North America, Taiwan, and Europe, anal sex is behind outbreaks among non-vaccinated MSM (*Ndumbi et al., Euro Surveill.* 2018;23:1700641).

In the United States, 2-3% of men acknowledge homosexual relationships (*Zaza et al., JAMA.* 316:2355-6). Likewise, a recent study from Switzerland reported that 3% of adult males (80,000 persons in a country population of 8.5 million people) were MSM (*Schmidt et al., Sex Transmit Infect*, in press). Targeting sexually active homosexual men with frequent periodic STI screening, education, and ensuring immunization for *N. meningitidis* and hepatitis A would be very cost-effective.

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Gene Editing for HIV Cure at the Edge

Whereas advances in antiretroviral therapy and its widespread use are providing huge benefits in terms of preventing new HIV transmissions to uninfected individuals as well as halting disease progression in patients, the elimination of HIV from carriers remains elusive and requires new approaches. Current estimates of 37 million people living with HIV worldwide represent an important stimulus for pursuing new strategies for HIV cure. Most researchers believe that genetics instead of any chemotherapy will bring the new path toward HIV elimination.

During the past 60 years, modern genetics has steadily evolved from diagnostics to therapeutics. In 1959, Jérôme Lejeune (1926-1994) reported for the 1st time that trisomy 21 was the cause of the Down syndrome. After this first discovery, several other chro-

mosomopathies and distinct genetic abnormalities that produce congenital human illnesses were identified. Genetic diagnosis steadily expanded from karyotypes to genes, a switch that was largely facilitated after a second major breakthrough in 2001, when complete sequencing of the human genome was achieved.

The latest major step in human genetics came in 2012, following the discovery of the CRISPR/Cas9 system as a mechanism for adaptive immunity in bacteria and archaea, and the recognition of its potential use for gene editing (*Jinek et al., Science* 2012;337:816-21). The door was open modifying the human DNA. Major ethical issues surrounding the use of this technology include off-target effects, germline consequences, and manipulation of human embryos when using *in vitro* fertilization experiments.

Two major CRISPR/Cas9 approaches are being examined as anti-HIV weapons (*Wang et al., Virus Res.* 2018;244:321-32). The first strategy focus on excision or mutational inactivation of the provirus within infected cells (*Kaminski et al., Sci Rep.* 2016;6:22555; Yin et al., Mol Ther. 2017;25:1168-86). Major challenges are accessing all body infected cells, proper delivery systems, and target-off effects.

A second CRISPR/Cas9 strategy against HIV aims to disrupting the CCR5 protein that acts as HIV entry cell receptor, precluding viral infection. The proof-of-concept for the success of this strategy derives from the "Berlin patient," one HIV-infected individual with leukemia that underwent bone marrow transplantation with donor CCR5-deficient cells. The virus was unable to infect the transplanted cells. A few years' later antiretrovirals were stopped, with no viral rebound. To date, the subject remains HIV-free. He is the only living person known to has cleared HIV infection (*Hutter et al., N Engl J Med.* 2009;360:692-8).

Therapeutic gene editing can be achieved at various developmental stages of the human being. First, it can be delivered into one-cell embryos or oocytes at the time of intracytoplasmic sperm injection, avoiding mosaicism. Second, it can be delivered into fetuses before birth. Third, *in vivo* gene editing can be achieved in newborns or adults using the appropriate vectors. Of note, gene editing *in utero* may also lead to correction of *de novo* mutations, which are generated in embryos/fetuses, rather than those inherited from parents before birth. Almost one-third of all genetic diseases is caused by *de novo* mutations. Using non-invasive prenatal diagnosis, *de novo* mutations can now be detected in the cell-free fetal DNA that circulates in the maternal blood. *In utero* gene, editing will allow for correction before birth and may be ethically more acceptable than editing embryos. Furthermore, edited genes in fetuses will not be germline transmissible unless germ cells are targeted.

At the end of 2018, Chinese scientist He Jiankui reported that two human twin girls had been born following *in vitro* fertilization of gene editing embryos from a progenitor male that was HIV-infected. CRISPR/Cas9 had been used on a bunch of pre-implanted embryos to block CCR5 production. The medical community responded unanimously that such kind of experiments should never be done again breaking all ethical issues. The absence of justification and regulation of gene editing, especially involving germline cells, could have devastating consequences for the human species (*Rosenbaum L., N Engl J Med.* 2019, in press).

Given that 2019 marks the 25th death anniversary of Jérôme Lejeune, one of the fathers of modern genetics, new findings on HIV cure using CRISPR/Cas9 could be viewed as an award recognition to his pioneer work. Lejeune identified the genetic abnormality accounting for the Down syndrome and hardly tried during his life to find a cure. Now, promising results for genetic illnesses are been generated with the CRISPR/Cas9 technology, including *in utero* or neonatally gene editing of Duchenne muscular dystrophy, metabolopathies such as phenylketonuria and deafness (*Rossidis et al., Nat Med.* 2018;24:1513-8).

During the past years of Lejeune's life - late 80s and early 90s - the AIDS epidemic was exploding with neither treatment nor cure on the horizon. Lejeune's reflection was always on the side of the patient, including the unborn person. His famous lecture "On the nature of men," pronounced when he received the William Allen Award, granted by the American Society of Human Genetics (*Lejeune, Am J Hum Genet.* 1970;22:121-8), is an impressive testimony about how ethics must guide human research. For his work, the US president JF Kennedy personally honored him with the Kennedy Prize.

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