2011

Addressing the Fertility Needs of HIV-Seropositive Males

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Brian A Levine, Sahadat K Nurudeen, Jennifer T Gosselin, Mark V Sauer. *Future Virology*. March 2011 v6 i3 p299(8).

Author's Abstract:

An increasing number of serodiscordant couples are utilizing advanced reproductive technologies to address their reproductive needs. Recent literature has demonstrated that it is not only technically possible but also safe to utilize sperm-washing techniques to allow for the creation of embryos, thereby preventing both horizontal and vertical transmission of HIV. This article addresses the strengths and weakness of various reproductive techniques and discusses our experience at Columbia University (NY, USA), the location of the largest HIV-focused fertility program in the USA.

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Keywords

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HIV; infertility; serodiscordant; sperm washing

Globally, the number of individuals living with HIV in 2008 was estimated to be 33.4 million [101] . Approximately 1.1 million of these individuals reside in the USA [102] . While there is no cure for HIV, current treatment options -â articularly antiretroviral therapies (ARVs) -â allow many HIV-positive individuals to lead relatively normal lives, with greatly improved average life expectancy [1] . No differently from uninfected couples, serodiscordant couples often wish to have children. These serodiscordant couples have a variety of reproductive options, each with its own set of attendant risks and probabilities for success. Variations in clinical practice may dictate levels of expense and inconvenience associated with these techniques. However, the common goal of each method is reducing the risk of transmission of HIV to the mother and child by segregating the virus from the gametes used to create the embryo.

Fertility desires & methods of conceiving

While approximately 10 years ago, slightly less than a third of HIV-seropositive individuals in the USA desired children in the future, more recent reports indicate an overall increased interest in childbearing among HIV-seropositive individuals in the USA and around the world; this is commensurate with the improved treatment and health of those living with HIV [2,3] . Other than adopting a child or using frozen donor sperm insemination, male-positive serodiscordant couples who wish to conceive have elected to use timed intercourse (thus, reducing exposure to single acts of sex), or to use sperm that has been prepared for intrauterine insemination (IUI) or *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI). Although timed intercourse may be the most cost-effective means to achieve pregnancy, in serodiscordant couples, it also carries the greatest risk of

HIV transmission. The estimated risk of seroconversion is approximately one in 1000-â2000 opposite-sex sexual encounters, or less than 1% per sexual encounter [4,5] . More specifically, a recent meta-analysis indicated a risk of 0.04-â0.38% per instance of sexual intercourse for female-to-male transmission and a 0.08-â0.30% risk per instance for male-to-female transmission [6] . As demonstrated, the risk of transmission from men to women is greater than that from women to men, and the risk of transmission most likely varies with levels of the HIV-positive partner'âs viral load [4,7] . Among 92 male-positive serodiscordant couples who conceived naturally through intercourse in one study, two women became HIV positive several months after becoming pregnant, and two other women became HIV positive after delivering their infants, with all four of these women indicating that they had not been using condoms regularly [8] .

Processed semen that utilizes density-gradient centrifugation and 'âswim-up'â techniques is routinely performed by embryology/andrology laboratories prior to either IUI or IVF, and these have become popular options for serodiscordant couples seeking to safely become parents. Performing IUI with semen processing to allow male-positive serodiscordant couples to conceive was first reported in 1990 by Semprini *et al.* [9] . After being diluted in medium, unfractionated semen samples are filtered to remove any fibers, microcalculus and mucinous debris. The remaining sperm sediment is then layered onto a linear gradient of solution and pelleted by centrifugation. The spermatozoa pellet, now separated from seminal plasma and seminal nonspermatozoa cells, is washed, overlaid with medium and incubated for 20-â30 min to allow motile spermatozoa to swim-up. The resulting supernatant containing motile spermatozoa is then collected [10-â13] .

This semen-processing method, which effectively both segregates HIV from the cellular fraction (lymphocytes) and free virus from the sperm fraction, is termed 'âsperm washing'â, and is still commonly used today with continued success.

The use of IUI or IVF with ICSI for treatment of HIV-positive patients differs between reproductive centers throughout the world. The lower cost and less-invasive approach of IUI is attractive to many couples, although this procedure has primarily been offered in Europe where use of IUI for infected men is not prohibited by law. A recent review of the experience at a reproductive center in the UK demonstrated that the choice between treatment options depends mostly on the patient'âs or couple'âs reproductive etiology [14] . In the USA, the Centers for Disease Control does not endorse the use of intrauterine insemination in serodiscordant couples, which has slowed the introduction of treating these couples owing to fear of civil, and possibly criminal, lawsuits among medical practitioners [15] . IVF with ICSI has been practiced instead, which avoids directly 'âinseminating'â with known viral risk and, over the past decade, has become the preferred methodology [16] . However, this method involves ovarian hyperstimulation, transvaginal oocyte removal under anesthesia, sperm washing, selection of the individual motile sperm and injection of the sperm directly into the oocyte for fertilization. Thus, this method has the advantage of reducing the risk of exposure to sperm carrying the virus but at the high cost of an IVF approach and the associated potential consequences of assisted reproductive technology (ART).

Although IUI and IVF-âICSI demonstrated great success in terms of minimizing risk of seroconversion,

IUI may be less effective compared with IVF in terms of pregnancy outcome results. For example, in a multicenter, retrospective analysis of 853 serodiscordant couples undergoing sperm washing with IUI, patients completed a total of 2840 cycles, with a resulting pregnancy rate per cycle of approximately 15%, and a delivery rate per cycle of 11.5%; there were no female seroconversions at 6 months post-treatment [17] . Another center reported a 19% pregnancy rate per IUI cycle, and a 13.5% delivery rate per cycle among 741 serodiscordant couples who completed a total of 2400 IUI cycles over a 4-year period [18] . However, these pregnancy and delivery rates are less than half of the success rates reported elsewhere for IVF-âICSI for serodiscordant couples, which is typical when comparing success of IUI versus IVF per treatment cycle in the general population [19] . Advocates of the IUI approach argue that the lower multiple birth rate, lesser cost and relative noninvasiveness of the method justify the low-technical approach. Yet, many couples may prefer the immediacy of results and the ability to bank supernumerary embryos, afforded only through IVF.

Sperm-washing technique common to IUI & IVF-âICSI

As mentioned previously, the basic process of density-gradient centrifugation of semen followed by sperm swim-up has been in use for more than 20 years to treat serodiscordant couples interested in having a child [13] . The method has been well described in serodiscordant couples seeking to use IUI or IVF-âICSI, amassing over 3000 reported cycles without known seroconversion in the uninfected female [13,19] . In both techniques, male partners produce semen specimens by masturbation.

When the specimen is being prepared for IUI, after the washing procedure, an aliquot of washed semen ([proportional to]â¼100 µÂµl) is commonly tested using PCR for detectable HIV RNA prior to the sample being used for treatment. In many programs, it is mandatory for couples to freeze a washed negative sample as a backup in case residual HIV is found in a post-wash sample that would otherwise necessitate cycle cancellation [20] . The resultant HIV-negative aliquot is injected using an insemination catheter into the uterine cavity.

Sperm freezing further reduces the amount of viable sperm recovered for later insemination. Owing to their findings demonstrating the disadvantageous effect of frozen-âthawed sperm-washed specimens on total motile sperm counts, the Assisted Conception Unit at the Chelsea and Westminster Hospital in London (UK) has pursued the use of fresh semen samples as often as possible. Their center has recently adopted a new laboratory protocol that uses two instead of three wash cycles after density-gradient centrifugation, and they only require the swim-up method for IUI cycles for male patients not receiving highly active antiretroviral therapy (HAART), with detectable viral loads or with semen samples with significant debris. The authors state that with the new laboratory protocol, they have noted a significantly higher proportion of total motile sperm available for IUI [14] .

Another potential limitation with IUI relates to the fact that many men with HIV often have oligoasthenospermia, which complicates the recovery process. The etiology of these altered sperm characteristics has yet to be deduced, although there are a number of hypotheses. In an analysis of approximately 200 HIV-infected men in which 91% were undergoing HAART therapy, it was found that semen samples were commonly abnormal, with semen volumes, percentages of progressive mobile

spermatozoa, total sperm counts and polymorphonuclear cell counts being decreased, while the pH values and spermatozoa multiple anomaly indices were increased [21] . The Assisted Conception Unit recently demonstrated that it is the semen analysis parameters that are more predictive of sperm-washing/IUI success compared with the male patient'âs HIV parameters [22] .

By comparing IUI with IVF-âICSI, one of the distinct advantages of IVF-âICSI is that only single, viable, motile and washed sperm are selected for use, as opposed to IUI, in which a cohort of millions of cells are selected. Furthermore, men with abnormal semen parameters, termed male-factor infertility, often have lower success rates with IUI therapy, and must ultimately resort to IVF-âICSI in order to improve fertilization. The lower per-cycle success rate usually results in additional IUI cycles and, thus, added exposure to the risk of infection as repetitive cycles accumulate.

In our practice (the Center for Women'âs Reproductive Care at Columbia University, CO, USA), we elected to adopt an IVF approach when initiating a program for serodiscordant couples in 1998 [23] . Our experience over the last 10 years with 420 consecutive cycles of IVF with ICSI revealed that the clinical pregnancy rate per embryo transfer was 45%, while the ongoing/delivered pregnancy rate per embryo transfer was 37% [19] . This is comparable to the general IVF (nondonor oocyte) outcomes at our center. More specifically, the clinical pregnancy rate per embryo transfer was approximately 50% in 2009 for a similar age group (35-â40-year-old patients), and the live birth rate per embryo transfer was approximately 34% across the same age group for 2008. It is important to note that, in our practice, there has never been a female seroconversion following IVF-âICSI, nor has there been an HIV infection in any of the 170 delivered offspring [19] . Success with IVF in general -â and also for this subset -â is highly dependent upon the age of the woman, with younger patients (<35 years old) being much more likely to succeed than their older counterparts [23] . Examining the HIV-serodiscordant patients, approximately 90% conceived successfully and delivered a child with three or fewer attempts, whereas women over 40 years were half as likely to experience pregnancy [24] .

Experience at Columbia University

At our center, HIV-seropositive men and their seronegative female partners can pursue having a family through HIV-negative-donor sperm insemination or through IVF-âICSI. IVF-âICSI has been offered to HIV-serodiscordant couples at Columbia University since 1997. In our first 10 years of experience, 258 male-positive HIV-serodiscordant couples presented for initial consultation, with 181 proceeding with treatment [19] . Since our previous report, we have had an additional 50 male HIV-serodiscordant couples present for consultation. To date, there have been 383 initiated fresh-egg donor and autologous IVF-âICSI cycles and 69 frozen-embryo transfer cycles at our center. A total of 189 clinical pregnancies and 113 deliveries have resulted from 143 serodiscordant couples.

When male-serodiscordant couples initially present to our center, they must complete a list of screening requirements before pursuing IVF-âICSI (Box 1). A female partner must be aware of her male partner'âs positive HIV status, and both partners are fully informed of the risks associated with IVF-âICSI and the risk of HIV transmission to the female partner and their potential offspring. Once an initial consultation has been performed and informed consent has been obtained, female patients may

continue with the completion of the remaining screening requirements, which include the standard infertility evaluation (day-2 follicle-stimulating hormone and estradiol; screening for HIV, gonorrhea, chlamydia, syphilis, hepatitis B and hepatitis C; a pelvic ultrasound and sonohysterogram or hysterosalpingogram). Male seropositive partners must be currently under the care of an infectious disease specialist without any signs of AIDS or worsening infection. Prior to starting treatment, they must demonstrate stable HIV viral loads (250 cells/mm^3) over a 6-month period. Standard infertility evaluation is also required, including blood screening for syphilis, hepatitis B and C; and a semen analysis to rule out possible male factor etiologies. Preferably, we advise men who are not currently on medication to begin HAART to reduce their viral loads prior to initiating therapy.

Previous studies have demonstrated that males with chronic HIV infection often have abnormal semen analyses and hypogonadism [24,25] . From 1998 to 2007, our center found 42% of the male seropositive patients to have an abnormal semen analysis with at least one parameter in the subfertile range [26] . Although having a semen analysis with values in the subfertile range may initially seem inconsequential owing to our treatment with ICSI, males with severe oligospermia (abnormally low sperm counts) must have a semen analysis confirming at least 1 million total motile sperm in order to provide a sufficient amount for use following the sperm preparation process. This process can lead to a reduction in sperm count of up to 1 log in comparison to unprocessed ejaculate [12,27] . Owing to the theoretical risk of blood contamination of the sample, our male seropositive patients are not offered testicular sperm aspiration. While two case reports from European centers that offer microsurgical epididymal sperm aspiration to seropositive males with azoospermia (absence of sperm in the semen) were able to confirm negative testing of retrieved sperm samples prior to ICSI, the number of cases is minimal and only one pregnancy has resulted thus far [28,29] .

For our male patients who meet the total motile sperm parameters, a fresh semen specimen is collected on the day of the oocyte retrieval. Semen preparation for ICSI involves a class II biologic hood using a modified density-gradient centrifugation and swim-up method to help remove nonspermatozoa cells infected with the virus [9,30] . Only the remaining motile spermatozoa found within the supernatant following this swim-up method are selected [31] . Currently available assays for detecting HIV-1 RNA or HIV-1 DNA in semen cells demonstrate false-positive rates of 18 and 19%, respectively, owing to the very low detection limits [32] . Unfortunately, this can lead to repeat semen collections, repeat testing and, ultimately, increased time and costs to patients. However, with real-time PCR, collection and processing of semen samples can occur in 1 day, eliminating the need for cryopreservation [32] . At our center, selected spermatozoa do not undergo repeat testing for the virus prior to ICSI. Using the same semen processing technique as our center, Politch *et al.* reported exclusion of HIV-1 from the motile sperm fraction in ’âspiked’â semen samples using HIV-1 concentrations exceeding those observed in individuals with advanced AIDS (1 million copies/ml) [33] . In this same study, HIV-1 was detected in some of the heavily concentrated samples (>1 billion copies/ml) and, for this reason, many centers advocate retesting samples prior to use [33] . One reproductive center in the UK performs repeat testing for detectable HIV RNA after sperm washing for IUI and IVF with ICSI [14] . This decision is based on the finding of 9.7% demonstrable virus found in pre- and post-wash IUI seminal samples of HIV-positive males undergoing HAART with undetectable viral loads at their center [14,22] . Although repeat testing occurs at many European centers, the

majority of the current research has not demonstrated detectable HIV in the supernatant following modified density-gradient centrifugation and use of the swim-up method in individuals who meet our viral-load criteria [10,11,33] . Embryo transfers occur on day 3 (eight-cell stage of development), or day 5/6 (blastocyst stage of development), in accordance with American Society for Reproductive Medicine (ASRM) guidelines. After their fresh embryo transfer, any remaining high-quality embryos can be cryopreserved for a future thawed embryo transfer if the couple desires [34] .

After embryo transfer, it is important to follow-up with patients to ensure that the female partner and her fetus/infant remain uninfected. HIV DNA PCR and HIV RNA PCR are the post-treatment testing methods of choice owing to their high sensitivity. Female patients who do not become pregnant or have spontaneous abortions are tested 3 and 6 months after the embryo transfer. Pregnant patients are tested at each trimester, delivery and 3 months postpartum. Infants born to our serodiscordant couples are screened at birth and 3 months of age. Our procedures, to date, have not led to any female seroconversions or infected offspring, which is consistent with other published research utilizing IVF-âICSI procedures for serodiscordant couples [35-â42] .

When is fertility treatment appropriate for discordant couples? Legal & ethical considerations

Although it is now generally accepted that fertility treatment should not be withheld from HIV-serodiscordant couples when appropriate treatment is available, this perspective has not always been endorsed, and this issue remains controversial [43] . More specifically, prior to the emergence of ARVs and before the extensive data on the safety of sperm preparation techniques to remove HIV were available, the Ethics Committee of the ASRM discouraged fertility treatment for serodiscordant couples using the HIV-infected male'âs sperm [44] . This stance was buttressed by a 1990 report by the CDC of a case in the USA involving improperly processed sperm that allegedly involved HIV transmission to a woman who was inseminated with her husband'âs sperm on three occasions in 1989, which did not result in a pregnancy [16] . In addition to concerns regarding possible transmission to the mother and child, the housing and processing of HIV-infected material creates a potential risk to staff as well as the uninfected gametes stored at a particular site [43] .

However, the argument hinging on risk has been losing ground with the decreasing risk for transmission owing to the implementation of ARVs, effective semen processing and fertilization techniques, and greater knowledge among patients about preventing the spread of HIV. The empirical data overwhelmingly support the safety and efficacy of IVF-âICSI in order to minimize risk and increase success rates [19] . Legally, while donating HIV-positive semen is criminalized in some states, several states are catching up to the current ASRM guidelines and empirical evidence demonstrating that fertility treatment should not be denied to serodiscordant couples [45] . States in which donation of HIV-positive sperm is permitted generally stipulate that insemination may only occur when appropriate medical guidelines are followed and with detailed informed consent provided by the female partner who is the recipient of the sperm [45] . For example, the California Senate recently passed a bill that allows an exception to the law that prohibits the use of donated sperm that is HIV or human T-lymphotropic virus-1 positive in the event that the sperm will undergo advanced reproductive

processing to reduce the risk of transmission, that the recipient receives prophylactic treatment to reduce risk of infection, and when both parties (sperm donor and recipient) provide informed consent [46] .

A legal argument in favor of provision of fertility services for serodiscordant couples notes that failure to do so could be considered discriminatory. The Americans with Disabilities Act (ADA) prohibits discrimination against individuals with physical or mental disabilities to the extent that individuals who are HIV positive are considered to fall within this category; withholding fertility treatment for these individuals would be barred [103] . Furthermore, the Supreme Court case of Bragdon versus Abbott set the precedent that HIV-positive individuals cannot be discriminated against for healthcare-related services (in this case, a dental office) [47] .

While the importance of protecting the rights of HIV-positive individuals is undeniable, others have raised the issue of the rights and welfare of the child being created through this process, in light of the possibility for premature paternal death [43] . However, the Ethics Committee of ASRM, has likened HIV in this context to autosomal recessive diseases, such as Tay-âSachs disease or cystic fibrosis, in that with appropriate testing and counseling, fully informed patients should have the right to choose to have their own biological children [48] . As such, this committee has argued that fertility services cannot be withheld on ethical grounds from individuals with chronic viral infections, including HIV, if a center has the resources to provide care. Moreover, the life expectancy of HIV-positive individuals has increased to more than 20 years after diagnosis, allowing HIV-positive fathers the opportunity to be fully involved in raising and caring for their children [1] .

In 2004, prior to the statement from ASRM, the Ethics Task Force of the European Society of Human Reproduction and Embryology (ESHRE) also confirmed that assisted reproduction for HIV-positive people is ethically acceptable, as long as suitable precautions are taken. However, they also recommended against treatment for serodiscordant couples at that time [14] . The UK'âs regulatory body for ART clinics, The Code of Practice of the Human Fertilisation and Embryology Authority, released a statement in 2003 confirming HIV-positive patients'â rights to pursue treatment in order to have a child free of the virus [104] . Treatment centers in the UK, with the support of this regulatory body, are expected to offer reproductive and specialist HIV counseling for HIV-positive individuals [104] . Similar to the USA, few centers in the UK have pursued the necessary laboratory techniques required to provide treatment to HIV-positive patients pursuing reproductive assistance [14] .

Future perspective

Given the minimal risk of viral transmission and encouraging pregnancy rates, fertility treatment for HIV-serodiscordant couples is an important endeavor. We can expect that an increasing number of patients will be requiring such advanced reproductive techniques. As the need for these resources grows, we anticipate an increase in the number of centers offering these treatments in order to meet the demand and, as a function of the increased popularity of these techniques, we expect that screening will become more consistent across centers; this will allow for the simplification of

treatment, referrals and consistency in research (e.g., facilitating meta-analytic studies).

With that said, it is important to remember that patients have options and that treatment plans must be tailored to each specific couple'âs needs. Unfortunately, the areas of the world with the highest rates of HIV/AIDS, such as sub-Saharan Africa, are also the areas with the least access to treatment for HIV and reproductive options for HIV-serodiscordant couples who wish to conceive. In these regions, timed intercourse in the setting of optimal ARV might be the best option.

In the USA, less than 3% of Society for ART-registered centers provide fertility treatment for HIV-discordant (or HIV-concordant-positive) partners [34] . Given the rising number of serodiscordant couples, we can expect that an increasing number of patients will be requiring such advanced reproductive techniques and fertility centers will need to expand the scope of their practices.

The future of the field of addressing the reproductive needs of the HIV population is extremely bright, and it is exciting to be able to offer multiple options to patients who were previously excluded from the reproductive community.

Box 1. Screening requirements for HIV-serodiscordant couples pursuing assisted reproductive technology.

Couple

*âª Provide informed consent

*âª Be practicing safe sexual intercourse (using condoms consistently)

*âª Have a standard infertility evaluation

*âª Undergo a normal physical examination (male and female)

*âª Female partners must be seronegative

*âª Be aware of partner'âs HIV status

*âª Undergo HIV, gonorrhea, chlamydia, syphilis, hepatitis B and hepatitis C testing

*âª Undergo pelvic examination (PAP smear and cervical cultures)

*âª Be tested for serum estradiol and follicle-stimulating hormone concentrations

*âª Undergo pelvic ultrasound

*âª Undergo hysterosalpingogram

Seropositive male partners

*âª Be under active medical surveillance by an infectious disease specialist

*âª Have plasma HIV RNA viral counts less than 50,000 copies/ml, stable over 6 months (preferably undetectable)

*âª Have a $CD4^+$ count of more than 250 cells/mm^3 (preferably >400)

*âª Have no evidence of AIDS or worsening infection

*âª If not well controlled, taking highly active antiretroviral therapy

*âª Undergo semen analysis with total motile sperm of at least 1 million

*âª Undergo blood screening for syphilis, hepatitis B and hepatitis C

Executive summary

Fertility desires

*âª With improved quality of life and life expectancy, largely owing to antiretroviral therapy for HIV, an increasing number of serodiscordant couples are interested in conceiving.

*âª These couples can pursue many avenues to parenthood, from timed intercourse to using advanced reproductive technologies, which minimize the chance of possible horizontal or vertical HIV transmission.

Timed intercourse

*âª Timed intercourse is the least expensive alternative, although it exposes the female partner to the greatest risk of transmission, which is estimated to be approximately less than 1% per sexual encounter.

Sperm preparation

*âª Processed semen with ultracentrifugation steps and 'âswim-up'â is routinely performed prior to intrauterine insemination (IUI) or *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

Intrauterine insemination

*âª IUI with prepared semen is associated with a lower financial cost and does not require oocyte retrieval or IVF. However, IUI is associated with a lower per-cycle success rate than IVF-âICSI, and

there is an added exposure to the risk of infection with repetitive cycles.

IVF-âICSI

*âª For IVF with ICSI, the semen is processed and selected sperm are injected into the egg under direct visualization.

Sperm characteristics

*âª In those undergoing HAART therapy, semen samples are commonly abnormal, with semen volumes, percentages of progressive mobile spermatozoa, total sperm counts and polymorphonuclear cell counts being decreased, while pH values and spermatozoa multiple anomaly indices were increased.

*âª HIV-1 viral DNA has been demonstrated in ejaculated abnormal spermatozoa in seropositive subjects.

Columbia University HIV treatment paradigm

*âª Our center has a standard procedure for working with serodiscordant patients, including screening and consultation of couples to ensure that the risk of transmission is minimized.

*âª Male seropositive partners must be currently under the care of an infectious disease specialist without any signs of AIDS or worsening infection.

*âª Procedures, to date, have not led to any female seroconversions or infected offspring.

Legal ethical considerations

*âª Concerns regarding risks of possible HIV transmission must be weighed against the rights of HIV-positive individuals to have the same opportunity to conceive that others have.

*âª Centers should consider the risk of transmission to the mother and child, as well as the fact that the storage and processing of HIV-infected material creates a potential risk to staff and the uninfected gametes stored at a particular site.

Future perspective

*âª There is an increasing need for advanced reproductive technologies for serodiscordant couples. While currently, less than 3% of Society for Assisted Reproductive Technologies-registered centers provide fertility treatment for HIV-discordant (or concordant-positive) partners, an increasing number of fertility centers are likely to offer HIV-specific treatment in the future in order to meet the increasing demand.

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.