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Modeling of Human Immunodeficiency Virus Modes of Transmission in Iran

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ABSTRACT

Background: Main technique to control acquired immunodeficiency syndrome (HIV) infection is the effective preventive programs among high-risk groups. Modeling is one of the effective methods where there is inadequate data. We used the modes of transmission (MOT) model to predict the transmission of HIV infection in Iran.

Methods: We systematically searched published and grey literature to find values for the input parameters of MOT in 2010. The data were discussed by experts before being fed into the model. Using the Monte Carlo simulation, we computed the 95% confidence interval (CI) for the outputs of the MOT.

Results: The MOT estimates that 9136 new HIV infections would have occurred in Iran in 2010 (95% CI: 6831, 11757). About 56% (95% CI: 47.7%, 61.6%) of new infections were among intravenous drug users (IDUs) and 12% (95% CI: 9.5%, 15%) among their sexual partners. The major routes of direct and indirect HIV transmission in Iran are unsafe injection (68%) and unprotected sexual contact (34% unprotected heterosexual and 10% homosexual) respectively. If current coverage for safe injection among IDUs increases from 80% to 95%, new HIV infections in this group would decrease around 75%.

Conclusion: IDUs remain at highest risk of HIV infection in Iran, so the preventive program coverage for IDUs and their spouses needs to be increased. As the sexual transmission of HIV contributes increasingly to the pool of new infections, serious measures such as harm reduction program are required to reduce sexual transmission of HIV among the relevant key populations.

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Introduction

The acquired immunodeficiency syndrome (AIDS) pandemic, in its third decade, continues to spread rapidly across the world, blind to gender, borders or sexual orientation¹. An estimated 33.3 million people were living with human immunodeficiency virus (HIV) in 2010 throughout the world; 2.7 million new HIV infections and 1.8 million HIV-related deaths². However, between 2001 and 2010, AIDS-related deaths increased more than doubled in East Asia (from 24 000 to 56 000)². HIV/AIDS is projected to become the third leading cause of death globally and the leading cause of disability-adjusted life years (DALYs) in low- and middle-income countries by 2030³.

In most countries in Middle East and North Africa (MENA), such as Iran, HIV prevalence is relatively low⁴. Nevertheless, it is forecasted that the HIV epidemic from 2002 to 2025 can reduce gross domestic product (GDP) by 0.2% to 1.5% per annum in some countries of the region, including Iran^{5,6}. UNAIDS and WHO estimates state that 460,000

(400,000 to 530,000) people were living with HIV, and 68,000 (55,000 to 84,000) people had become newly infected with HIV in MENA in 2008. According to the same estimate, 92,000 (74,000 to 120,000) people were living with HIV in Iran which stands in contrast with the 22,000 cases so far recorded in the country^{2,4,7}.

HIV modes of transmission seem to have changed in Iran over time⁴. The first wave of HIV infection in Iran was among the recipients of blood products, however, an intensive blood screening program has effectively eliminated this mode of transmission⁸. At present, the HIV epidemic is concentrated among injecting drug users (IDUs) and driven by unsafe injecting practices⁹. IDUs account for 69.7% of all registered cases of HIV infection¹⁰, but HIV prevalence in this population has apparently stabilized at around 15%¹¹, on the back of an extensive harm reduction program that operates both inside and outside prisons^{10, 12, 13}. Although there has been an increase in the number of registered new HIV infections attributed to

sexual transmission, the behavioral and socio-cultural correlates of this emerging epidemiological trend have not been fully elucidated in a country where sex before or outside of marriage, including indirect and direct sex work, is highly stigmatized^{9, 14, 15}.

For effective management and planning on prevention and control of HIV, attending to the changes in the pattern of transmission and identifying the prime high-risk groups are highly crucial alongside focusing on the HIV/AIDS epidemic in the country and the patterns of its changes longitudinally¹⁶. The number of HIV cases in Iran is increasing daily and WHO is emphasizing on the importance of predicting the infection pattern and circumstances in the country. Moreover, there is a lack of accurate and valid information about pattern of transmission of HIV infection Iran. Accordingly, we designed the modes of transmission (MOT) model to identify the most important high-risk groups and the major MOT in Iran, and also compare the result with countries that ran the model^{17, 18}. This hopefully could contribute effectively to the preparation and implementation of HIV prevention programs in Iran^{14, 15, 19}.

Methods

We employed the MOT model in 2009 to predict the anticipated distribution of new HIV infections among the 15-49 year age group of the population based on the exposure groups in the subsequent year in Iran in 2010¹⁹. The MOT model

classifies population within the 15-49 yr age group into 13 groups based on the most prominent means of exposure to HIV, such as IDUs, female sex worker (FSW), clients of FSW, men who have sex with men (MSM), casual heterosexual sex (CHS), partners of high-risk groups (Table 1). It is worth noting that prisoners are one of the HIV exposure groups due to their high-risk behaviors but the MOT model has not considered them as a separate group. Modes of transmission needs four parameters including (a) size of exposure groups and general population age between 15 and 49 yr, (b) prevalence of sexually transmitted infections (STIs) within high-risk groups (as the likelihood of HIV infection transmission through sexual contact rises as much as four times when adjacent to STIs²⁰), (c) HIV prevalence in exposure groups and the general population, and (d) risky behavior parameters in three general categories. These categories are (1) the average of the number of partners in one year, (2) the average of the number of high-risk behaviors per partner in one year, and (3) the percentage of protected acts. Each class is defined differently in accordance with the group exposed. The last parameter is transmission probability affected by STIs and male circumcision (MC). The latter lowers by almost 60% the probability of HIV transmission from females to males^{21, 22}. As the MOT model is adapted from UNAIDS, this study has applied the probabilities of HIV transmission as recommended by UNAIDS.

Table 1: Definitions of Exposure Groups

Groups	Definitions
IDUs	Individuals who have had drug injection at least once in the past year and the most important means of transmission of the HIV infection was needle sharing.
FSWs	Women who have offered sexual services at least once in the last year in return for money, food, accommodation, or anything else.
Clients of FSWs	Men who have had sexual contact with FSWs in return for money, food, accommodation, or anything else.
MSM	Men who have had sexual contact with another man at least once in the last year.
Casual Heterosexual Sex (CHS) group	Individuals who have had more than one sexual partner in the last year.
Partners of IDUs, partners of clients of FSWs, female partners of MSM, partners of CHS group	Individuals who have had one sexual partner in the last year, and whose partners are allocated to the IDUs, clients of FSWs, MSM or CHS risk groups.
Individuals engaging in low-risk heterosexual sex	Individuals who have had one heterosexual sex partner in the last year and their partners have also had only one heterosexual sex partner in the last year. This group consists of individuals in monogamous partnerships that are not only faithful to their partners, but their partners are faithful to them, and their partners are neither IDUs nor MSM.
Individuals at no risk	Individuals who have had no sexual partners in the last year. This may be a result of primary abstinence (never had sexual intercourse) or secondary abstinence (had sexual intercourse in the past, but are not sexually active currently).
Recipient Medical injections	This study assumes that the total population of 15-49 is within those who receive medical injections.
Recipient Blood transfusions	Individuals who have received blood transfusion in the last year.

STIs prevalence required for the MOT model among high-risk groups (excluding the fixed sexual partners of the four high-risk groups of IDUs, clients of FSWs, MSM, CHS group, and the adult population receiving medical injections and blood).

A partner in the IDU group is defined as an individual with whom one shares a needle in the process of drug injection. Among the recipients of blood and intravenous medicine, the number of one has been designated for the number of partners per annum. For the other high-risk groups indicated in the model, the term partner refers to a sexual partner and the

prevention means of HIV infection within this group is using condom.

In the IDUs group, the probability of infection transmission in one injection with a syringe contaminated with the HIV is considered. Among sexual partners IDUs, CHS, MSM and clients of FSW there is the probability of the infection transmission from a male to female (and from a female to a male) in a sexual contact without condom. In the MSM group, there is the probability of infection transmission from male to male in anal intercourse without using condoms.

The data needs for an MOT study are summarized in Table 2, used in our study. To obtain accurate information on the required parameters in this model, a systematic method of review was employed. The timeframe for conducting the studies for the search was determined to be 2005 to 2009. Of course, the databank produced by the end of summer 2010 was also updated.

Table 2: Data type and data source used for mode of transmission studies³¹,

Data type	Usual data source
Population size	Surveillance; Ministry of Health statistics
HIV prevalence	Surveillance
STI prevalence	Special studies
Number of acts	BSS ^a
Number of partners	DHS ^b , BSS ^a
Percent protection	DHS ^b , BSS ^a , service statistics
Transmission probability	Literature

^a Behavioral surveillance studies;

^b Demographic and health surveys

In the first step we searched main national and international databases such as Magiran, SID, Irandoc, Iranmedex, and Pubmed using HIV/AIDS, venereal, sexual contacts, sexual behavior, sexual, drug abuse, drug injection, needle sharing, unsafe injection, addiction, injecting addiction, female sex worker, prostitute, unsafe sex, prison, blood recipient, and blood transfusion as searching keywords, using connective word (or, and). Then, we searched medical journals manually based on the list of the entire journals on the website of the Research and Technology Deputy ranked as scientific-research periodicals, Ministry of Health and Medical Education (MOHME). At that time we searched grey literature including proceedings of medical symposia, projects, theses and dissertations of medical students and MOHME reports and statistics and relevant governmental and international administrations such as the Islamic Republic of Iran Law Enforcement, the Drug Control Headquarters, the Department of Blood Transfusion, the Department of Welfare, and the United Nations Office on Drugs and Crime (UNODC) in Iran.

To this end, the final report and documentations used in the HIV assessment project commissioned by the MOHME and the Centre for Disease Management and conducted by an independent team ending in 2009 were also used. In addition, the documentations and also a number of the parameters used in other modeling studies of the country such as HIV estimation and projection document conducted in 2009²³, were used. After that, we contacted HIV/AIDS experts either directly or indirectly and used their guidance and documentations.

In the next step, after substantiating relativity of the paper with the goals of this study, the quality criteria were assessed based on standard quality evaluation forms^{14, 24}. The criteria relate to the validity of the study methods (design, sampling frame, sample size, outcome measures, measurement and response rate), interpretation of the results and applicability of the findings.

Once the quality of the studies was assessed, all the data pertaining to each parameter was disaggregated by high-risk subgroups inputted into an Excel spreadsheet designed for this very purpose alongside the features of the study used. The parameters for which there were no data obtained were also specified.

To gain more data on the parameters for which accurate data is not available in Iran (such as the data on MSM), the documents of other countries which are similar to Iran in terms of their circumstances (such as Pakistan) and other states which have used this model (such as Morocco) were reviewed. Furthermore, the information on each parameter of the MOT model in these countries was summarized in comparative tables.

Due to limited access to comprehensive and reliable data on certain required parameters during the systematic review and also because of the discrepancy of the data in some cases, we conducted in-depth interviews and focus group discussions with key individuals involved in National AIDS Programs in the MOHME, Ministry of Welfare, and Drug Control Headquarters. In these interviews, we presented our findings, and sought their estimations on the parameters. In these discussions, experts explored the validity of studies, their generalizability of their findings and also consistency between results. After discussions, we asked them to give their best estimate of each parameter, compatible with the abstracted information from Iran and other countries. Since there were disagreements over some of the parameters, the participants were asked to give ranges instead of exact values.

The MOT model is deterministic and to estimate the anticipated incidence, the constant values of each parameter is required, whereas with respect to the data in Iran – as noted earlier – and the uncertainty in the values of the parameters required for the model and consequently the definition of a reasonable ranges for each of them, precise estimates cannot be reached. To address this shortcoming, one of the most accurate means of simulation which is the Monte Carlo analysis was employed. In this calculation procedure, random cases of the probability distribution functions are repeated. As a result, hundreds or thousands of output data are generated and through the calculation of the mean and the upper and lower ranges it enhances the accuracy in analysis and the range which shows the uncertainty level.

For that reason we used Monte-Carlo simulation to compute confidence intervals for the outputs and to create the pessimistic and the optimistic possible scenarios. As most of the parameters measured in the model were continuous, Monte Carlo simulation was undertaken assuming a Normal distribution. As we had just a range for each parameter, we computed the standard deviation (SD) for each parameter using the following simple formula:

$$SD = (\text{maximum value} - \text{minimum value}) / 6$$

For each required parameter (with a mean and SD of its own) a random variable with a normal distribution has been constructed and repeated 10,000 times. Then we generate 10,000 iterations for each formula in MOT spreadsheet to estimate the number of new HIV infections in each key population for simulation. We subsequently combined the values of the parameters in each iteration. Finally, we computed the modes and 95% confidence interval (CI) based on the 2.5 and 97.5 percentiles. To cross-validate our outputs, we compared the predicted number of new infections with the outputs of the 2010 Estimation and Projection Project for Iran regarding the overlap between CI of the estimates generated by the two models.

We performed statistical calculations using Stata version 10, (StataCorp LP, TX, USA). We cross-checked our results by repeating parts of the procedure in Microsoft Excel 2007.

Results

We estimated through the MOT model that 9136 new HIV infections would have occurred in Iran in 2010 (95% CI: 6831, 11757). Based on this model, around 56% (95% CI: 47.7, 61.6 %) of the new infections occur in IDUs and 12.2 % (95% CI: 9.5, 15 %) in their sexual partners. FSW, their clients, and their fixed partners or spouses account for 1.3%, 4.2%, and 2.8% of new HIV infections respectively, whilst MSM and their female partners account for 10.9% and 4.9% of the new cases respectively. In addition, low-risk heterosexuals account for 8.1% of the new HIV cases. It appears that no new cases of HIV infection occurred among blood recipients and those who take medical injections. Casual heterosexual sex altogether accounts for only 0.62 % of new cases (Table 3).

Table 3: Predicted number of new HIV infections per key population and their 95% CI.

Adult Risk Behavior	Population (x1000)	Incidence (number)	95% CI
Intravenous Drug users	200	5112	3914, 6442
Partners of Intravenous Drug users	100	1110	798, 1342
Female Sex Workers	60	116	70, 175
Clients of Female Sex Workers	1200	381	291, 519
Partners of Female Sex Workers clients	600	259	203, 319
Men who have Sex with other Men	300	908	593, 1380
Female partners of Men who have Sex with other Men	150	456	331, 597
Casual Heterosexual Sex	1500	27	23, 39
Partners of Casual Heterosexual Sex	750	29	23, 33
Low-risk heterosexual	34000	738	585, 911
No risk	4130	0	0, 0
Medical injections	43050	0	0, 0
Blood transfusions	60	0	0, 0
Total	86100	9136	6831, 11757

Figure 1 presents the incidence of HIV per 100,000 populations. The highest rate of incidence is among IDUs and their fixed sexual partners. This figure shows that the highest limit of the 95% CI of incidence rate pertains to IDUs; the low limit of the incidence in this group is also higher than that of other groups.

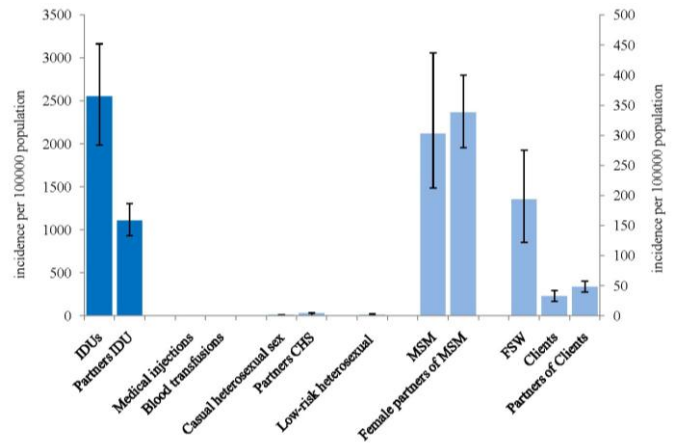


Figure 1: HIV incidence in key populations at highest risk per 100,000 (with 95% CI); the error bars represent the input data. The incidence in all groups appears on the right hand side of the figure excluding IDUs and their sexual partners

The results indicated that unsafe injection – direct or indirect (through sexual contact between HIV positive IDUs and their wife or their sexual fixed partners) – bears a role in almost 68% of the new cases of HIV infection among the 15-49 yr age group of Iran. Meanwhile, around 15.4% of the new cases of the infection within this population are transmitted (directly and indirectly) through sexual contact with the same sex. On the other hand direct contribution of unsafe injection, heterosexual contact, and homosexual intercourse to HIV incidence among Iranian adults was 55%, 35%, and 10% respectively.

We also investigated how changes in service coverage would affect the incidence. If coverage of needle-syringe programs were to increase from 80% to 95%, then HIV incidence in IDUs would decrease by 75%. If condom coverage among the sexual partners of IDUs were to increase from 30% to 95%, there would be a 93% decrease in the number of new HIV infections within this key population (Figure 2A and 2B).

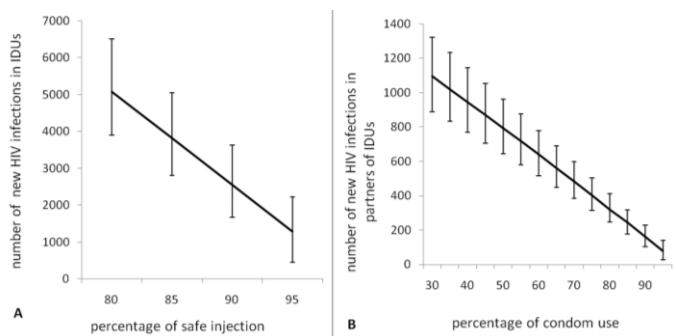


Figure 2: Impact of increasing safe injection coverage on human immunodeficiency virus (HIV) incidence among Intravenous Drug users (IDUs) (A) and the impact of increasing condom use coverage on HIV incidence among the sexual partners of IDUs (B).

The results also demonstrated that if condom use coverage among MSM and their fixed female sexual partners increases by 30% (from 65% to 95%) and 80% (from 10% to 90%) respectively, approximately 89% of the new HIV infections in each of these groups would be prevented.

Discussion

We estimated that approximately 9136 new unknown HIV infections would have occurred in Iran in 2010. This figure is

compatible with the main findings of the HIV MOT modeling through the estimation and projection package (EPP) software for the 2009 to 2014²³ such that the number of new cases in 2010 was estimated to be around 7100 and the CI of the estimates generated by the two models overlap. Around 68% of new HIV infections would occur among IDUs and their sexual partners; this implies that unsafe injection remains the principal mode of HIV transmission in the country. Unprotected heterosexual (34%) and homosexual transmissions (10%) come next on the list while zero new infections are projected to occur through either blood transfusion and blood products or unsafe medical injections.

Our finding of 9000 new infections represents almost 2000 more cases than what previously estimated, (EPP)²³. Although we cannot rule out overestimation by the MOT model, it seems that, given the greater precision of the MOT input data (due to access to the data of recent surveys in defining MOT inputs), the observed difference is because of the mathematical constants and/or equations used in the model. But we note that the uncertainty levels of the two estimates overlap and so the difference is not statistically significant.

Despite the implementation of harm reduction programs among IDUs, the latter remains the population at highest risk of HIV infection in Iran. Even though the population of IDUs is smaller than that of other most-at-risk groups, the efficiency of HIV transmission in this group means that harm reduction programs need to scale up coverage even further²⁵⁻²⁷. The second-highest number of new infections is seen among the spouses or 'steady partners' of IDUs. Assuming a monogamous or quasi-monogamous relationship, the principal risk of HIV transmission comes from unprotected sex with the IDU partner. Harm reduction programs should be complemented by voluntary counseling and testing, focusing on sexual transmission, STI management, and condom access. Although there is no evidence to indicate that HIV prevalence among MSM has exceeded the 5% threshold, the estimates derived from this MOT exercise need to be confirmed by integrated bio-behavioral surveillance studies.

The number of HIV infections among FSWs is lower than IDUs but the incidence rate (per 100,000 persons) shows that the risk of an HIV epidemic in this group is possible. This premise is reinforced by early indications that HIV prevalence among FSW might reach the critical level (5%) in the following years if no control program changes the trend. Combined with the predicted number of new infections among both clients and partners of FSW, a new "bridging" scenario is seemingly emerging in Iran. Given the heterogeneous and highly fluid nature of sex work in Iran^{28, 29}, appropriately structured and targeted harm reduction programs are needed for this key population. Although existing small-scale efforts are clearly a step in the right direction, they need to be scaled up and diversified if they are to mitigate the HIV epidemic in this setting.

In addition to the aforementioned groups, an important point to emerge is that 21% of new HIV infections occur in the spouses/partners of people at highest risk of HIV infection (IDUs, MSM, clients of FSWs, and CHS). Although most of these individuals might have no risky behaviors, the indirect but significant risk to which they former are exposed can best be reduced by a combination of counseling and testing, consistent condom use, and periodic screening and

management of sexually transmitted infections. Moreover, a small percentage of new HIV infections occur in the CHS group, but this should not breed complacency; 60% of Iranian population aged 15 to 49 years and sexually active. Different studies have reported an increase in sex before and outside marriage^{28, 30}. Given this apparent shift in socio-cultural norms, HIV incidence could increase sharply in this age group in the next few years; a situation which requires taking serious attention.

We showed that increasing the coverage of harm reduction programs among IDUs has the greatest downward effect on the number of new HIV infections. An increase in safe injection coverage from 80% to 95% would reduce the number of new HIV infections by 75% in this group, and by 40% in the 15-49 years population. This is a significant effect and a strong reason to invest further in harm reduction programs. In key populations at highest risk of sexual transmission, especially the partners of individuals at high risk, increasing condom use by 20% would reduce HIV incidence in the 15-49 yr age group by 16%. These results establish a convincing argument in favor of consolidating harm reduction programs as well as counseling and training on condom usage in these groups, particularly the permanent sexual partners of these high-risk groups.

Comparing the results of the MOT model in Iran with other countries (such as Kenya, Thailand, Uganda, and Morocco) proved that the rate of incidence per 100,000 population in the Iranian adults was higher than that of Morocco and lower compared to that of Uganda, Thailand, and Kenya. While Kenya and Uganda have generalized epidemics, the epidemic is concentrated in Morocco, Thailand, and Iran¹⁶⁻¹⁸.

The percentage of HIV transmission through unsafe injection in Iran (56%) is higher compared to other countries. Although the percentage of HIV infection transmission through unprotected heterosexual sex is lower in Iran (34%) compared to other countries, the percentage of new HIV infections transmitted through homosexual male sex in Iran (10%) is higher compared to that of Kenya and Uganda.

The portion of HIV transmission through sexual contact in Iran was lower than that of other countries and this mode of transmission is not as considerable as needle sharing. Nevertheless, sexual transmission of HIV must not be overlooked.

The quality and accuracy of input data for model was appropriate for IDUs but much less so for FSW and MSM in particular. This shows that how research has focused overwhelmingly on the key populations at greatest risk of HIV infection, namely IDUs, often at the expense of other populations at high risk. This is one of the main limitations of our study. We drew extensively on expert opinion to fill in gaps in the input data, building consensus around conservative estimates to minimize bias due to absent data. The MOT model categorizes individuals based on their main exposure to HIV, and does not take into account the distribution of behaviors within groups, the patterns of mixing by demographic, social, geographic, and economic variables and the influence of specific sexually transmitted diseases. In other words, the outputs are only as reliable as the input. The model also does not generate estimates for the under 15-year age group, considered among those vulnerable to HIV.

The overlap between FSWs and IDUs is also considerable, making it difficult to estimate the exact number of people involved in both risky injection and sexual behavior. This limitation of our model may have resulted in an overestimation of HIV infection in FSWs.

The MOT model does not address prisoners as a distinct group, who are considered as such in Iran. The project was nevertheless conducted by dividing the population of prisoners between other key populations, and it does not appear to have fundamentally affected the overall number of probably infected individuals and the estimates. We need prison-specific estimates to assist the prison healthcare services better to focus their efforts and program on HIV/AIDS prevention.

Since we used standard software developed by UNAIDS, we did not have enough facilities to estimate the bias of the results and to apply more sophisticated statistical methods. However the software are using frequently and its results are available in UNAIDS website (www.unaids.org) for many countries.

The actual data of HIV incidence based on solid evidences are rarely available even within the developed countries therefore they are estimated using models; in this way even back estimations are the only available information for policy makers as scientist.

Conclusion

Unsafe injection among IDUs is still the main mode of transmission. Coverage of harm reduction of services must be raised by 15% in order to decrease the number of new infections by 75% and a special focus should be put on the spouses and permanent partners of IDUs and MSM as well as FSWs and their clients. These two groups which may have not been enough attention to them in nationwide programs must be prioritized.

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Conflict of interest statement

Authors declared that they have no conflict of interest.

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