Effect of Highly Active Antiretroviral Treatment (HAART) During Pregnancy on Pregnancy Outcomes: Experiences from a PMTCT Program in Western India

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Abstract

Previous research regarding the effect of highly active antiretroviral treatment (HAART) on pregnancy outcomes shows conflicting results and is predominantly situated in developed countries. Recently, HAART is rapidly being scaled up in developing countries for prevention of mother-to-child transmission (PMTCT). This study compared adverse pregnancy outcomes among HIV infected women (N = 516) who received either HAART (N = 192)—mostly without protease inhibitor—or antepartum azidothymidine (AZT) with intrapartum nevirapine (N = 324) from January 2008 to March 2012 through a PMTCT program in western India. We analyzed the effect of HAART on preterm births, low birth weight, and all adverse pregnancy outcomes combined using univariate and multivariate logistic regression models. Women on HAART had 48% adverse pregnancy outcomes, 25% preterm births, and 34% low birth weight children compared to respectively 32%, 13%, and 22% among women on AZT. Women receiving HAART were more likely to have adverse pregnancy outcomes and preterm births compared to women receiving AZT. Preconception HAART was significantly related to low birth weight children. This study demonstrated increased risk of adverse pregnancy outcomes with protease inhibitor excluded HAART. Prospective studies assessing the impact of HAART on MTCT as measured in terms of HIV-free survival among children are needed.

Introduction

While the benefits of highly active antiretroviral treatment (HAART) for prevention of mother-to-child transmission of HIV (PMTCT) are undisputed, there have been some concerns regarding its possible adverse effects on pregnancy outcomes. Maternal HIV infection has been associated with adverse pregnancy outcomes; however, there are conflicting data regarding the effect of HAART during pregnancy on pregnancy outcomes. While there is an increasing number of studies that suggest higher risk of preterm birth (PB) (<37 weeks)1–7 and low birth weight (LBW)2,8–10 among babies of women receiving HAART during pregnancy, there are also some studies that did not observe this association.11–16 Most of the studies are from developed regions6,17–19 and only recently research findings are emerging from developing regions.7,20–22 Previous research from developed regions assessed the role of HAART containing protease inhibitors (PI), whereas the recent studies from developing regions have also evaluated the effect of PI excluded HAART on pregnancy outcomes (Table 1). Overall, studies have reported that HAART given to HIV-infected pregnant women in the first trimester (<13 weeks of pregnancy),21,23–25 Containing PI20,26–28 and given to women with severe immunosuppression22 is associated with PB.

Despite the conflicting outcomes on pregnancy outcomes, HAART is being rapidly scaled up in developing countries for PMTCT following conclusive studies demonstrating its efficacy in reducing mother-to-child transmission of HIV (MTCT). Use of HAART can reduce MTCT to <2% from the possible 25–30% in the absence of any intervention.30 With the possibility of achieving such low rates of MTCT, the Joint United Nations, along with partners, have called for “virtual elimination” of MTCT; that is, reduction of the number of new pediatric HIV infections by 90% between 2009 and 2015 and reduction of MTCT rates to <5% worldwide.31 As a result of

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the global efforts to provide universal access to PMTCT services with more effective protocol, the proportion of women receiving antiretroviral medicines (ARVs) excluding single dose nevirapine (sd-NVP) for PMTCT increased from 34% in 2008; Europe; (N=19585*) to 61% in 2011 worldwide.32 With increasing expansion of HAART in developing countries and with previous conflicting results of its effect on pregnancy outcomes, which mainly focused on developed countries, it is essential to understand the effect of ARVs on pregnancy outcomes in these developing countries for better planning and delivery of PMTCT services at the micro and macro levels.

The objective of this article is to compare the risk of adverse pregnancy outcomes (APO) among HIV-infected women (N=516) who received either HAART (N=192) or antepartum azidothymidine (AZT) with single dose intrapartum nevirapine (sd-NVP) (N=324) through a private sector PMTCT program in Maharashtra, Western India, between January 2008 to March 2012. We distinguished preterm births (PB), low birth weight (LBW), and all adverse pregnancy outcomes (PB, LBW, non-live births) combined (APO) as outcomes to compare the effect of ARV protocol.

### Methods

#### Setting

The data used in this study were collected prospectively in a PMTCT program implemented by PRAYAS, a nongovernment organization located in the city of Pune, in Maharashtra State of India. Maharashtra has been one of the high HIV prevalence states in India (HIV prevalence in 2010 was 0.55%).33 The PRAYAS PMTCT program was initiated in 2002 with the support from Elizabeth Glaser Pediatric AIDS Foundation (EGPAPF) and is primarily being implemented in the private health sector. More than 65% of India’s population access health care in the private sector for their general health care needs.34 The program currently reaches approximately 36,000 pregnant women annually through 50 hospitals in 10 districts of Maharashtra. Since

### Table 1. Summary of Selected Recent Literature on HAART and Pregnancy Outcomes from Developing and Developed Regions

<table>
<thead>
<tr>
<th>Author; year; region; (N)</th>
<th>ART protocol</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Developing regions</strong></td>
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<tr>
<td>Chen et al;7 2012; Africa; (N=9504)</td>
<td>NVP/AZT/3TC; LPV/rt/AZT/3TC; AZT monotherapy</td>
<td>Women receiving preconception HAART had higher odds of PB (AOR: 1.2; CI: 1.1–1.4), SGA (AOR: 1.8; CI: 1.6–2.1) and SB (AOR: 1.5; CI: 1.2–1.8). Initiating HAART in pregnancy (versus AZT) was associated with higher odds of PB (AOR: 1.4; CI: 1.2–1.8), SGA (AOR: 1.5; CI: 1.2–1.9), and SB (AOR: 2.5; CI: 1.6–3.9).</td>
</tr>
<tr>
<td>Powis et al;20 2011; Africa; (N=560)</td>
<td>ABC/AZT/3TC; LPV/rt/AZT/3TC</td>
<td>PI based HAART was most significant factor for preterm birth (AOR: 2.03; CI: 1.26–3.27)</td>
</tr>
<tr>
<td>Marazzi et al;21 2011; Africa; (N=3273)</td>
<td>NVP based HAART; no ART</td>
<td>HAART reduced maternal mortality, PB and abortion/still birth. However, it had no significant effect on birth weight.</td>
</tr>
<tr>
<td>Machado et al;22 2009; Brazil; (N=696)</td>
<td>2 NRTIs; NNRTI based HAART; PI-based HAART; AZT monotherapy</td>
<td>Pre-conception HAART was associated with an increased risk of PB (AOR: 5.0; CI: 1.5–17.0) and LBW (AOR: 3.6; CI: 1.7–7.7)</td>
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<tr>
<td><strong>Developed regions</strong></td>
<td></td>
<td></td>
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<tr>
<td>Lopez et al;17 2012; Europe; (N=519)</td>
<td>NNRTI based HAART; PI-based HAART;</td>
<td>Increased risk of both spontaneous (AOR: 2.1; CI: 1.5–3.0) and iatrogenic (AOR: 3.2; CI: 8–5.7) PB among HIV infected women. However, use of HAART especially in second half of the pregnancy was associated with iatrogenic PB but not with spontaneous PB</td>
</tr>
<tr>
<td>Townsend et al;5 2010; USA and Europe; (N=19585*)</td>
<td>Monotherapy; dual therapy; HAART</td>
<td>Compared with monotherapy, HAART was associated with increased risk of PB in ECS (AOR: 2.4; CI: 1.49–3.86) and NSHPC (AOR: 1.43; CI: 1.10–1.86) but not in PSD (AOR: 0.92; CI: 0.67–1.26). Heterogeneity in the association was not explained by study design but may have been the result of substantial population differences. Pooled analysis showed increased PB with HAART</td>
</tr>
<tr>
<td>Patel et al;18 2010; USA and Puerto Rico; (N=777)</td>
<td>HAART with PI; HAART without PI</td>
<td>HAART with PI was not significantly associated with PB compared with HAART without PI (AOR: 1.22; CI: 0.70–2.12)</td>
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<tr>
<td>Grosch-Woerner et al;19 2008; Europe; (N=183)</td>
<td>Monotherapy; dual therapy; HAART</td>
<td>HAART exposure during pregnancy was associated with an increased risk of PB (AOR: 3.40; CI: 1.13–10.2) compared with monotherapy.</td>
</tr>
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</table>

ABC, abamune; AOR, adjusted odds ratio; CI, 95% confidence interval; ECS-European Collaborative Study; LBW, low birth weight; LPV/rt, lopinavir boosted with ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NSHPC, National Study of HIV in Pregnancy and Childhood; NVP, nevirapine; PB, preterm birth; PI, protease inhibitor; PSD, Pediatric Spectrum of HIV Disease project; SB, still birth; SGA, small for gestational age; 3TC, Lamivudine; *Sample size combined for all three databases.
its inception, the program has provided comprehensive antenatal care (ANC) counseling to 255,000 pregnant women attending ANC clinics. After informed consent, 215,000 pregnant women were tested for HIV, and 1600 HIV infected women were provided PMTCT services as per the then contemporary WHO recommended protocols. After registration in the program, HIV-infected women were followed every month until the assessment of HIV status of the exposed baby by DNA PCR at the age of 4 months if receiving replacement feed, or at 3 months after cessation of breastfeeding. Women were informed about breastfeeding, as well as replacement feeding, and were provided support in deciding and continuing the chosen infant feeding option. Before 2010 WHO guidelines, exclusive breastfeeding and early cessation of breastfeeding was recommended to women choosing to breastfeed. However, after the recent WHO infant feeding guidelines (2010), the program recommends exclusive breastfeeding until 6 months and, introducing appropriate complementary foods thereafter, and continues breastfeeding for the first 12 months of life. Prophylactic ARV during this period of breastfeeding is provided to reduce the risk of transmission.

Screening of partners and other children was encouraged and, if detected to be HIV infected, they were linked to HIV care. Since 2008, all the HIV-infected women enrolled in the program underwent baseline CD4 cell counts, with repeat testing every 6 months. In addition, some women underwent plasma HIV viral load testing (by RNA PCR), if required for their treatment.

Data on demographic indicators, obstetric history, HIV testing, co-morbidities, and treatment were collected at the time of registration of pregnant women in the PMTCT program and data on pregnancy outcomes and adherence to treatment protocol were recorded during follow-up visits. These data were collected by trained counsellors in structured case report forms at the hospitals and were compiled centrally as a part of regular program monitoring. Case to case data validation was regularly conducted as a part of internal monitoring of the program, and these data were entered in special software that was developed for monitoring the PMTCT program.

Study population

HIV-infected women who were registered in the program from January 2008 to March 2012 (N=742) were considered for analysis as CD4 counts were offered to all infected women from this date. Women who were still pregnant at the time of data compilation (N=43), who had opted to terminate their pregnancy voluntarily (N=25), who died (N=3), or were lost to follow-up before delivery (N=39), who reported twin births (N=7), and who did not receive any antenatal ARV due to late presentation in ANC (women who received only sd-NVP) (N=109) were excluded from the analysis. Thus, in total, 516 women with reported pregnancy outcomes were included in the final analysis (Fig. 1).

We distinguished two groups of women according to ARV protocol: women on HAART versus women on AZT. As per the then contemporary WHO guidelines, HAART was initiated to women who required treatment for their own health depending on their CD4 counts (<350) and disease stage, otherwise AZT was given along with sd-NVP in labor. Note that women who presented late were offered only sd-NVP during labor as per the guidelines and they are not included in this study.

Outcome measures

The effect of HAART on pregnancy outcomes was analyzed using three outcome indicators. Preterm Birth was defined as when the child was born at <37 weeks of gestation; low birth weight was defined as babies having birth weight <2500 g, and...
A combined indicator of all adverse pregnancy outcomes (APO) was estimated if the child was born before term (<37 weeks) or had low birth weight (birth weight <2500 g) or if the pregnancy did not result in live birth (spontaneous abortions and stillbirths). Gestational age was recorded by clinicians based on ultrasound test (USG) or last menstrual period (LMP) at the time of delivery. Birth weight was taken soon after delivery mostly in the labor room. The data on gestational age and birth weight were collected on a separate delivery note completed by the clinician after delivery. All women considered for this analysis delivered at health facilities. Women who reported non-live births (N=21) were excluded from the analysis of PB and LBW children. Data on birth weight were missing for 14 cases mostly because the child was not weighed at birth, either due to home delivery or if the child died immediately after birth.

Explanatory variables

The data on explanatory variable such as demographic factors (age, education, occupation, socio-economic status), obstetric factors (weeks of pregnancy at the time of registration in the program, parity, past intrauterine death, and level of anemia) and HIV related factors (CD4 counts, past opportunistic infections, symptoms of STI during current pregnancy) were collected at the time of registration of the women in the program. Other variables such as duration and adherence of ARV medicines, and Hb% were documented during follow-up visits.

Statistical analysis

The differences among women who received HAART and those who received AZT in terms of pregnancy outcomes (PB, LBW, and non-live births), HIV-related factors, obstetric factors, and demographic factors were assessed using chi-square tests. The effect of ARV protocol on pregnancy outcomes was analyzed using independent univariate and multivariate logistic regression models for all three outcome variables, the latter by including all other background HIV-related, obstetric, and demographic variables. Data were analyzed using SPSS (version 20).
<table>
<thead>
<tr>
<th></th>
<th>Preterm birth (PB)</th>
<th>Low birth weight (LBW)</th>
<th>All adverse pregnancy outcomes</th>
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<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
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</tr>
<tr>
<td>HAART</td>
<td>2.343 (1.459–3.762)</td>
<td>3.350 (1.520–7.383)</td>
<td>2.029 (1.400–2.941)</td>
</tr>
<tr>
<td>AZT</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–200</td>
<td>2.320 (1.095–4.917)</td>
<td>1.211 (0.422–3.471)</td>
<td>2.417 (1.290–4.526)</td>
</tr>
<tr>
<td>201–350</td>
<td>1.353 (0.716–2.559)</td>
<td>0.882 (0.375–2.071)</td>
<td>1.371 (0.844–2.229)</td>
</tr>
<tr>
<td>351–500</td>
<td>0.806 (0.405–1.601)</td>
<td>0.917 (0.441–1.909)</td>
<td>1.013 (0.617–1.662)</td>
</tr>
<tr>
<td>≥500</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>16–20</td>
<td>2.167 (0.851–5.519)</td>
<td>3.370 (1.031–11.012)</td>
<td>2.827 (1.329–5.986)</td>
</tr>
<tr>
<td>21–25</td>
<td>1.232 (0.540–2.811)</td>
<td>1.192 (0.449–3.161)</td>
<td>1.603 (0.609–4.121)</td>
</tr>
<tr>
<td>26–30</td>
<td>1.354 (0.573–3.200)</td>
<td>1.598 (0.592–4.312)</td>
<td>1.365 (0.556–3.327)</td>
</tr>
<tr>
<td>≥31</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
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<tr>
<td>Preterm delivery</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>3.850 (2.357–6.287)</td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>-</td>
<td>3.795 (2.149–6.704)</td>
</tr>
</tbody>
</table>
Results

Of the 516 women who reported pregnancy outcome, 37% (192) received HAART and 63% (324) received antenatal AZT (Fig. 1). Comparison of the profile of women according to the protocol they received is given in Table 2. In general, any adverse pregnancy outcome (APO) was observed among 45% women, 17% children were born preterm, and 27% children had LBW. Significantly higher proportion of women who received HAART had children born preterm, had LBW children and non-live births (Table 2). Average gestational age of babies born to women who received HAART was 37.47 weeks (95% CI, 37.11–37.82) and 38.22 weeks (95% CI, 38.06–38.39) among women who received AZT. Eleven per cent of the women had advanced immunological suppression (CD4 <200) at the time of pregnancy and almost all were from the HAART group. Among the HAART group, 71% had CD4 >200 at the time of pregnancy which is due to receiving HAART prior to conception and related improvement from this treatment. Among the 17% of women who had opportunistic infections in the past such as tuberculosis, herpes zoster, and oral candidiasis, a significantly higher proportion of women were in the HAART group (31% vs. 8%, p=0.000). A higher proportion of women who received HAART had registered early in their pregnancy and had 3rd or higher order parity (36% vs. 26%, p=0.001) compared to women who received AZT. Severe to moderate anaemia (<10 g/dL) was observed among 39% of the women and there was no statistically significant difference according to the protocol they received. The mean age of women was 25 years (SD±4.5 years). The mean age of women who received HAART was significantly higher (27 years, SD±4) than women who received AZT (25 years, SD±4) (p=0.000). Sixteen per cent of women had no education, 21% had remunerated activity, and 36% were from poor socioeconomic backgrounds; there was no statistically significant difference among women in both the groups.

Crude and adjusted risk ratios (RR) of ARV protocol and significant variables for PB, LBW, and APO are shown in Table 3. In the univariate model, women who received HAART and had CD4 count <200 were significantly more likely to experience PB, have LBW children, and experience APO compared to women who received AZT and who had CD4 count >500, respectively (Table 3). In the multivariate model after controlling for the effect of HIV related, obstetric, and demographic factors, women who received HAART were 3.4 times more likely [RR 3.350, 95% CI 1.520–7.383] to experience PB and 1.9 times more likely [RR 1.949, 95% CI 1.099–3.454] to experience APO in comparison to women who received AZT. Younger women (age 16–20) were also 3.4 times more likely [RR 3.370, 95% CI 1.031–11.012] to experience preterm birth in comparison to the older women (age ≥31).

Discussion

Women who received HAART—mostly without PI—were 3.4 times more likely to experience preterm birth and 1.9 times more likely to experience all adverse pregnancy outcomes in comparison to the women who received AZT with sd-NVP, after controlling for the effect of other HIV-related, obstetric, and demographic factors.

Effects of HAART on increased preterm birth have been documented from developed countries in Europe and USA5,6,17,21 and recently from Africa11,23,36 This is the first study from India to demonstrate increased risk of preterm birth among children born to women receiving HAART during pregnancy. Average weeks at the time of delivery among women who received HAART was 37.74 (95% CI, 37.11–37.82) and 38.22 (95% CI, 38.06–38.39) among women who received AZT and very preterm births (between 26–32 weeks of pregnancy) was observed among 13 children, all but one were born to women who had received HAART. The rates of preterm birth observed in this study (25% in HAART and 13% in AZT group) were similar to the rates observed in Mma Bana study in Botswana.23 However, women in the Botswana study were randomized to receive the PI-based protocol. One of the studies from Maharashtra India37 compared pregnancy outcomes among HIV-infected women (not on HAART) with HIV-uninfected women and reported no statistically significant differences in pregnancy outcomes in both the groups. This substantiates the findings of our study that HAART could be a potential risk factor for preterm birth.

Our study—along with a few others9,25—has demonstrated the increased risk of adverse pregnancy outcomes, particularly PB, among children of women who received other than a PI-based combination. The majority of the women receiving HAART in our study were taking 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) combination (97%) and only 6 women received PI-based combination. The initial studies investigating the effect of HAART on preterm birth have indicated increased risk of PB, mostly with PI-based combination ART where the effect of PI was compared with NRTI and NNRTI combination.22,23

The risk of having babies with LBW was higher among women who received HAART compared to women who received AZT. However, this relationship was not statistically significant in the multivariate analysis. Nine per cent of the all babies (N=41) had very low birth weight (<2000 g) with significantly higher proportion among women who had received HAART (13%) compared to women who had received AZT (6%) (p=0.006). In an additional multivariate analysis that distinguished women taking HAART prior to conception (N=61) and HAART initiated during antenatal period (N=131), preconception HAART was significantly associated with increased risk of LBW [AOR 2.843, 95% CI 1.261–6.409] compared to antenatal AZT.

The association of preconception HAART and LBW among babies has been reported earlier for Botswana,11,30,38 Brazil,22 and Cote d’Ivoire.9 In the study by Parekh et al.10 from Botswana which compared antenatal AZT with HAART, preconception HAART was associated with very-small-for-gestational births but not with PB, whereas another study from the same country that assessed the effect of in utero exposure of HAART on longitudinal growth of uninfected children found significant LBW among infants exposed to HAART as compared to AZT-exposed infants.31 The study also concluded that lower weights in HAART exposed uninfected infants were rapidly corrected during the first 6 months of life.31 While the exact pathophysiological mechanism of preconception HAART and LBW is not known, there is a need for further prospective studies that would also account for important predictors of birth weight such as maternal nutrition status. The data on maternal nutritional status, which is one of the known predictors of birth weight,39 were lacking in our study.
Women who received HAART were more likely to experience any adverse pregnancy outcome. A combined indicator of adverse pregnancy outcome, which also included spontaneous abortions and stillbirths in addition to PB and LBW, was estimated in order to assess the overall magnitude of adverse pregnancy outcome with respect to the protocol. A previous study based on data from the third round of the National Family Health Survey in India has shown that the risk of spontaneous abortions and still births is higher among HIV infected women who were unaware about their HIV status, compared to HIV-negative women. However, limited research is available on the effect of HAART on fetal death and a recent pooled analysis of studies showed that HAART did not reduce the possibility of stillbirths.

In our study, in spite of the better CD4 counts at the time of pregnancy due to treatment (HAART), the group of women who received HAART might be clinically different than the women who received AZT. However, a recent study by Bar-oncelli and colleagues among women who were diagnosed before pregnancy and undergoing ART at conception reported that women who have not experienced AIDS-defining events have similar maternal and neonatal outcomes as compared to women with more advanced stage of the disease. Thus it is less likely that a past history of AIDS defining illness would affect pregnancy outcomes.

This study has demonstrated a high risk of adverse pregnancy outcomes, particularly preterm birth, among HIV-infected Indian women receiving HAART not containing PI through a private sector PMTCT program in Maharashtra. The reliability of the data was checked consistently during the program implementation. However, the possibility of certain measurement errors, particularly in recording birth weight, cannot be ruled out as the measurements were taken by different people and the measuring device was not standard across sites. Despite these limitations, the results clearly indicate the need for further in-depth prospective study to determine the magnitude of adverse pregnancy outcomes among HIV-infected women receiving HAART and the health care needs of these children.

The Indian national program for prevention of mother to child transmission is likely to rollout HAART (option B). While the benefits of HAART must be provided to pregnant women, there is a need to address certain knowledge gaps associated with rolling out HAART for PMTCT. Well-designed prospective studies are needed to understand the impact of HAART on MTCT as measured in terms of HIV-free survival among children. Adherence to HAART during pregnancy and in postpartum period, which was shown to be significantly lower in one of the recent studies in Latin America, should be assessed among Indian women.

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Author Disclosure Statement

No competing financial interests exist.

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