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Using a Composite Maternal–Infant Outcome Measure in Tuberculosis-Prevention Studies Among Pregnant Women

Grace Montepiedra,[1] Soyeon Kim,[2] Adriana Weinberg,[3] Gerhard Theron,[4] Timothy R. Sterling,[5] Sylvia M. LaCourse,[6] Sarah Bradford,[7] Nahida Chakhtoura,[8] Patrick Jean-Philippe,[8] Scott Evans,[9] and Amita Gupta[10]

[1]Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA, [2]Frontier Science Foundation, Boston, Massachusetts, USA, [3]University of Colorado, Denver, Colorado, USA, [4]Stellenbosch University, Cape Town, South Africa, [5]Vanderbilt University Medical Center, Nashville, Tennessee, USA, [6]University of Washington, Seattle, Washington, USA, [7]FHI 360, Durham, North Carolina, USA, [8]National Institutes of Health, Bethesda, Maryland, USA, [9]The George Washington University, Washington, DC, USA, and [10]Johns Hopkins University, Baltimore, Maryland, USA

Background. Tuberculosis (TB-)-preventive therapy (TPT) among pregnant women reduces risk of TB in mothers and infants, but timing of initiation should consider potential adverse effects. We propose an analytical approach to evaluate the risk–benefit of interventions.

Methods. A novel outcome measure that prioritizes maternal and infant events was developed with a 2-stage Delphi survey, where a panel of stakeholders assigned scores from 0 (best) to 100 (worst) based on perceived desirability. Using data from TB APPRISE, a trial among pregnant women living with human immunodeficiency virus (WLWH) that randomized the timing of initiation of isoniazid, antepartum versus postpartum, was evaluated.

Results. The composite outcome scoring/ranking system categorized mother–infant paired outcomes into 8 groups assigned identical median scores by stakeholders. Maternal/infant TB and nonsevere adverse pregnancy outcomes were assigned similar scores. Mean (SD) composite outcome scores were 43.7 (33.0) and 41.2 (33.7) in the antepartum and postpartum TPT initiation arms, respectively. However, a modifying effect of baseline antiretroviral regimen was detected ($P = .049$). When women received nevirapine, composite scores were higher (worse outcomes) in the antepartum versus postpartum arms (adjusted difference, 14.3; 95% confidence interval [CI], 2.4–26.2; $P = .02$), whereas when women received efavirenz there was no difference by timing of TPT (adjusted difference, .62; 95% CI, −3.2–6.2; $P = .53$).

Conclusions. For TPT, when used by otherwise healthy persons, preventing adverse events is paramount from the perspective of stakeholders. Among pregnant WLWH in high-TB-burden regions, it is important to consider the antepartum antiretroviral regimen taken when deciding when to initiate TPT.

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Keywords. risk-benefit analysis; prioritized composite outcomes; tuberculosis; pregnancy.

Pregnant and early postpartum women, especially those living with human immunodeficiency virus (HIV) in high-tuberculosis (TB-)-burden areas, are at particular risk for developing TB [1–3]. The global burden of TB among pregnant women is substantial, with about 150 000 estimated to have developed TB in 2019 [2], and both mothers and their infants have negative sequalae [1]. Tuberculosis-preventive therapy (TPT), such as isoniazid (INH), has been shown to be efficacious in reducing the incidence of TB among persons living with HIV, those recently exposed to an infectious pulmonary TB case, and those with latent TB infection [4]. Studies of therapies such as TPT among pregnant women, however, have focused on safety, given the assumption that interventions that are efficacious in nonpregnant adults implies that the same would hold true for pregnant women [5, 6]. For interventions in pregnancy, comprehensive safety concerns include (1) maternal adverse events (AEs), (2) infant AEs, and (3) adverse pregnancy outcomes, which are typically assessed separately. In the case of TPT, there is potential benefit to the infant so that an additional key interest is efficacy of maternal TPT to reduce infant TB incidence. A major challenge in interpreting the results is how to synthesize these separate comparisons and make a final risk–benefit evaluation. Moreover, separate analyses of disaggregated outcomes do not usually capture the overall clinical experience of the mother–infant pair, or take into account correlations between clinical outcomes in the mother and the infant. For example, AEs are expected to be positively correlated in women and their fetuses/infants (ie, when the woman has an AE the fetus/infant is also more likely to have one), thus the deleterious effects are compounded. Additionally, maternal death during pregnancy may be considered worse than during the

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Correspondence: G. Montepiedra, Center for Biostatistics in AIDS Research, 651 Huntington Avenue, FXB 517 Boston, MA 02115 (gmontepie@sdac.harvard.edu).

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postpartum period because it results in fetal demise. To address these considerations, a composite outcome can be used to examine safety and efficacy in the mothers and their infants simultaneously. The composite outcome may rank or score the mother–infant pairs relative to one another based on the overall clinical experience of the pairs.

Several methods for combining and analyzing multiple outcomes simultaneously have been proposed in the statistical and clinical literature. Chuang-Stein et al [7] introduced the idea of combining safety and efficacy into a ranked outcome. Generalized or variant approaches of this outcome, and accompanying analysis strategies, ensued [8, 9] and include the desirability of outcome ranking (DOOR) by Evans et al [10]. Another approach assigns weights or partial scores to different components (or combinations thereof) and incorporates them in a composite outcome [11–14]. Applications related to these methods have been seen in clinical outcomes data [15, 16], including outcomes from TB clinical trials [17]. Rogozinska et al [18] developed composite outcomes considered to be important for assessing the effect of diet and lifestyle during pregnancy.

In this paper, we show how the composite outcome approach may be adopted for TPT clinical trials or observational cohorts among pregnant women to account for the overall outcome in mother–child pairs. Using a focus group to inform the development of a 2-stage survey, we describe how we developed maternal–infant composite outcomes that allows a unified risk–benefit assessment of an intervention. We then apply this approach to assess the timing of initiation of INH TPT (IPT) in pregnant versus postpartum women (that is, immediate INH vs deferred INH initiation) in an analysis of data from the TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants (TB APPRISE) trial, which was the first and only large randomized controlled TB-prevention trial conducted in pregnant women [19]. This study was designed primarily to confirm whether initiating IPT during pregnancy is safe for the mother compared with deferring initiation to 12 weeks postpartum. Efficacy in the mother and her infant as well as infant AEs were also evaluated as key secondary outcomes. Given that the immediate INH group in that study had higher rates of some AEs while the deferred INH group had higher rates of other AEs, an overall risk–benefit assessment could not be readily made, because the comparative importance of outcomes had not been scored and/or ranked in the initial trial outcome analyses. The addition of a composite maternal–infant outcomes (scores or ranks) analysis incorporates their relative importance and provides the overall comparison.

METHODS

Construction of the Composite Outcome

The construction of the composite outcome was performed before the results of the trial were disseminated to the TB APPRISE study team and the public. The process was based on the Delphi method [20], a structured, iterative procedure in which a panel of experts answer questionnaires to reach a consensus opinion. Our approach involved a focus group followed by a 2-stage survey of 26 stakeholders. Details are provided in the Supplementary Material and Supplementary Tables 1–3. The final developed composite outcome is described in Table 1, with each possible mother–infant paired event included in 1 of 8 categories. Paired events in the same category are assigned the same score or rank.

Statistical Analysis of Data From TB APPRISE

P1078/TB APPRISE was a double-blinded, placebo-controlled TB-prevention trial that randomized 956 pregnant women living with HIV on antiretrovirals (ARVs) to receive 28 weeks of IPT initiated either at study entry during pregnancy (immediate INH group) or deferred to 12 weeks after delivery (deferred INH group). Women and their infants were followed up to week 48 postpartum. The primary objective of the trial was to determine whether initiating IPT at antepartum is noninferior to deferring initiation to 12 weeks postpartum with respect to maternal safety, with the primary outcome defined as treatment-related grade 3 or higher [21] maternal AEs. Key secondary objectives included separate comparisons of the 2 treatment groups with respect to infant safety, adverse pregnancy outcomes, and efficacy measured by incident TB in mothers and in infants.

For this analysis, each mother–infant pair was assigned a score according to the derived composite scoring system (as described in Table 1) based on relevant events that occurred during the study. Each mother–infant pair was also assigned a rank (see Table 1) corresponding to the paired event describing the worst outcome that each person in the pair experienced.

The mean composite scores of mother–infant pairs were compared between treatment groups using a 2-sample t test. The composite ranked outcomes were compared between treatment groups using a Wilcoxon rank-sum test. The potentially moderating effect of the baseline (study entry) ARV regimen in the treatment group comparison of the composite scores was assessed using an interaction model. A multiple regression model of the composite scores on either treatment group or interaction between treatment group and baseline ARV regimen was performed, with the following predefined maternal baseline characteristics considered as potential covariates: maternal age, status of the surface antigen of the hepatitis B (HBsAG) virus, hepatitis C serology, CD4 count, plasma HIV RNA, interferon-γ release assay status, midupper arm circumference, twin pregnancy, current smoker, food insecurity, and cotrimoxazole use. Covariates with P values less than .15 in univariate regression models were included in the multiple regression model. Comparisons between study arms, as well as modification effect of the ARV regimen, were considered to be statistically significant if corresponding estimates were associated with a P value less than .05.

Table 1. Composite Maternal-infant Outcome[c] Score/Rank

Grouping	Maternal Event	Fetus/Infant Event	Score	Rank
A	Postpartum death[d]	Death[d]	100	8
	Death during pregnancy[d]	…	100	8
	Postpartum death[d]	TB[d]	100	8
	TB	Death	100	8
	Postpartum death[d]	Severe adverse pregnancy outcome[a,d]	100	8
	Postpartum death[d]	Adverse pregnancy outcome[b,d]	100	8
	Postpartum death[d]	Grade 3 or 4 AE[d]	100	8
	Grade 3 or 4 AE	Death	100	8
B	Postpartum death[d]	No event[d]	90	7
	No event	Death	90	7
	TB[d]	Severe adverse pregnancy outcome[a,d]	90	7
C	TB[d]	Adverse pregnancy outcome[b,d]	80	6
	TB[d]	Grade 3 or 4 AE[d]	80	6
	Grade 3 or 4 AE	TB	80	6
	Grade 3 or 4 AE[d]	Severe adverse pregnancy outcome[a,d]	80	6
	Grade 3 or 4 AE[d]	Adverse pregnancy outcome[b,d]	80	6
	No event[d]	Severe adverse pregnancy outcome[a,d]	80	6
D	TB[d]	TB[d]	75	5
E	TB[d]	No event[d]	70	4
	No event	TB	70	4
	Grade 3 or 4 AE[d]	Grade 3 or 4 AE[d]	70	4
F	No event[d]	Adverse pregnancy outcome[b,d]	65	3
G	Grade 3 or 4 AE[d]	No event[d]	60	2
	No event	Grade 3 or 4 AE	60	2
H	No event[d]	No event[d]	0	1

Abbreviations: AE,adverse event; LBW,low birth weight; PTD, preterm delivery; SLBW,severely low birth weight; SPTD, severely preterm delivery; TB,tuberculosis.

[a]Includes stillbirth or spontaneous abortion, SPTD, SLBW, and major congenital anomaly.

[b]Includes PTD and LBW.

[c]Combinations of maternal-infant events.

[d]Maternal-infant events were categories included in the second-stage survey (Supplementary Table 3).

RESULTS

There were 926 mother–fetus/infant pairs in TB APPRISE where the mother delivered her infant (alive or otherwise) during the study. Each of these mother–infant pairs was assigned a score based on their experience in TB APPRISE, using the composite maternal–infant score defined above (Table 1). For example, if the mother died postpartum and the infant was delivered with severely low birth weight, this falls under group A and the mother–infant pair would be assigned a score of 100 for the composite outcome. Table 2 shows the frequency distribution of scores (and corresponding ranks) of the 926 mother–infant pairs, by treatment group. The observed average ranks of mother–infant pairs in the data, based on their composite outcome scores, are also provided. The mean composite outcome scores were compared between treatment groups by the *t* test. Note that this is equivalent to comparing the observed average ranks between groups by the *t* test. The mean (SD) scores were 43.7 (33.0) and 41.2 (33.7) for the immediate INH and deferred INH groups, respectively. Although the mean was slightly higher (worse) in the immediate INH group, there was no significant difference between arms (difference = 2.6; 95% confidence interval [CI], −1.8 to 6.8; $P = .25$). In addition, the distribution of ordinal categories by arm (Table 2) was compared using the Wilcoxon rank-sum test. No significant difference between the study arms was detected ($P = .18$).

Table 3 shows the results of univariable regression models of the maternal–infant composite score on each of the potential covariates, the unadjusted model for the interaction between treatment group and ARV regimen, and the multiple regression model with treatment group by ARV regimen interaction and important covariates. For the interaction model, the parameter estimates compare immediate versus deferred INH within ARV regimen (classified by the non-nucleoside reverse transcriptase inhibitor in the regimen). The interaction effect was significant in the model adjusted for baseline covariates ($P = .049$). Among women who were on nevirapine (NVP)-containing antiretroviral therapy (ART) at study entry, the composite score was generally higher (indicating lower desirability) among those assigned to the immediate INH group than to the deferred INH group (difference = 14.3; 95% CI, 2.4–26.2; $P = .02$), whereas among women on an efavirenz (EFV)-containing regimen at study entry, there was no difference in average scores between the 2 INH treatment groups (difference = 1.5; 95% CI, −3.2 to 6.2; $P = .53$) (see Table 3, Supplementary Table 4, and Figure 1).

Table 2. Distribution of Composite Mother–Fetus/Infant Paired Outcomes in the TB APPRISE Study

Maternal–Fetus/Infant Category	Composite Outcome Score	Composite Outcome Average Rank[a]	Composite Outcome Rank	Frequency (%)		Cumulative Frequency[b] (%)	
				Immediate INH (n = 460)	Deferred INH (n = 466)	Immediate INH (n = 460)	Deferred INH (n = 466)
A	100	921.5	8	3 (0.7)	7 (1.5)	460 (100.0)	466 (100.0)
B	90	904.0	7	10 (2.2)	15 (3.2)	457 (99.3)	459 (98.5)
C	80	843.0	6	60 (13.0)	37 (7.9)	447 (97.2)	444 (95.3)
D	75	…	5	0 (0.0)	0 (0.0)	387 (84.1)	407 (87.3)
E	70	758.5	4	34 (7.4)	38 (8.2)	387 (84.1)	407 (87.3)
F	65	686.0	3	40 (8.7)	33 (7.1)	353 (76.7)	369 (79.2)
G	60	495.5	2	152 (33.0)	156 (33.5)	313 (68.0)	336 (72.1)
H (no event)	0	171.0	1	161 (35.0)	180 (38.6)	161 (35.0)	180 (38.6)
Score: mean (SD)	…	…	…	43.7 (33.0)	41.2 (33.7)	…	…

Abbreviation: APPRISE, Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants; INH, isoniazid; SD, standard deviation; TB, tuberculosis.

[a]Average rank for mother–infant pairs in the trial data with the same score.

[b]Proportion less than or equal to score.

Table 3. Regression Model for Composite Maternal–Fetus/Infant Outcome Score (Higher Score Is Worse) for the TB APPRISE Study

Predictors and Group[a]	Univariable Results			Multivariable results		
	Slope[b] Estimate	95% CI	*P*	Slope[c] Estimate	95% CI	*P*
Study arm/ARV regimen at baseline interaction			.07			.049
EFV-containing regimen at baseline: immediate INH – deferred INH	1.2	(−3.5, 5.9)	.62	1.5	(−3.2, 6.2)	.53
NVP-containing regimen at baseline: immediate INH – deferred INH	13.1	(1.2, 25.1)	0.04	14.3	(2.4, 26.2)	0.02
HBsAG positive vs negative	7.3	(4.3, 18.9)	.22	…	…	…
Hepatitis C positive vs negative serology	10.6	(−11.5, 35.6)	.35	…	…	…
CD4 count (cells/mm^3) (per 10 cells higher)	−.04	(−.1, .05)	.33	…	…	…
HIV RNA < LLQ vs ≥LLQ	−6.2	(−10.7, −1.8)	.006	−6.7	(−11.2, −2.1)	.004
Maternal age (years) (per year of age)	−.2	(−.6, .2)	.35	…	…	…
Midupper arm circumference (ref: obese >31) (in cm):			.04			.02
Malnourished: <23	13.3	(2.3, 24.2)	.02	15.1	(3.7, 26.6)	.01
Normal: 23–31	−.5	(−5.3, 4.4)	.85	−.3	(−5.2, 4.5)	.88
Initiated cotrimoxazole before or at study entry vs never	3.7	(−.7, 8.0)	.10	4.8	(.4, 9.2)	.03
Current vs never/previous smoking	9.5	(−6.5, 25.5)	.25	…	…	…
Food insecure vs not food insecure	1.2	(−5.2, 7.7)	.71	…	…	…
Twin pregnancy vs singleton	21.2	(1.4, 41.0)	.04	20.5	(−.2, 41.2)	.052

All models included gestational age strata (parameter estimates and *P* values not shown as gestational age was a stratification factor in the randomization). *P* values for overall tests and for covariates with >2 levels relative to the reference category are from *F* tests. Reference categories are omitted.

Abbreviations: APPRISE, Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants; ARV, antiretroviral; CI, confidence interval; EFV, efavirenz; HBsAG, hepatitis B surface antigen; HIV, human immunodeficiency virus; INH, isoniazid; LLQ, lower limit of quantification; NVP, nevirapine; ref, reference; TB, tuberculosis; TB APPRISE, TB Ante vs. Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants.

[a]For the study arm/ARV regimen at baseline interaction, the difference between immediate and deferred INH are provided by receipt of an EFV- or NVP-containing regimen at baseline.

[b]Unadjusted regression coefficient (if categorical, this is the difference in mean score from the reference group).

[c]Adjusted regression coefficient was adjusted for parameter estimates shown. For study arm–ARV regimen interaction, slope estimates are for pairwise comparisons of immediate vs deferred INH within ARV groups.

For mothers who were on an NVP-containing regimen, being randomized to antepartum IPT resulted in worse overall outcomes for the mother–infant pairs compared with those randomized to postpartum IPT. To understand what accounted for this difference, Supplementary Table 4 provides a breakdown of the frequency of paired maternal–fetus/infant events between study arms, stratified by antepartum ARV regimen. Among women who were taking an NVP-containing regimen at entry, compared with the postpartum IPT arm, the antepartum IPT had higher frequencies in nearly all the negative outcomes groups (ie, groups B, D, F, and G maternal–fetus/infant outcome categories [favoring postpartum IPT]) slightly lower frequency in group C (favoring antepartum IPT), substantially lower frequencies in group H (no negative maternal–fetus/infant outcomes; 25.4% vs 44.3%, favoring postpartum IPT), and no outcomes in group A (death in mother or fetus/infant) and group D (TB in both) for either the antepartum or postpartum IPT arm. When women were taking NVP-based ART there were more mother–infant pairs in the immediate arm in which AEs were experienced by the mother and/or the fetus/infant.

In contrast, among women who were taking EFV-containing ART, even though more of those randomized to postpartum IPT experienced the worst composite outcomes (ie, group A events [death in mother or fetus/infant]), these were very small percentages of the pairs (0.8% vs 1.8% favoring antepartum IPT). Women who were taking EFV-containing ART also had more group B and group E outcomes in the postpartum IPT arm. However, the differences favoring antepartum IPT were offset by more events in groups C and F in the antepartum IPT arm, favoring deferred IPT. The overall result was no difference in composite outcomes by timing of IPT for women taking EFV-based ART.

A post hoc analysis suggests that mother–infant pairs in the antepartum IPT/NVP subgroup also had worse outcomes overall than mother–infant pairs in the antepartum IPT/EFV subgroup (estimated difference in adjusted composite outcome scores of −10.1; 95% CI, −19.2 to -1.00) and those in the postpartum IPT/EFV subgroup (−12.1; 95% CI, −21.2 to −3.0).

The adjusted analysis also showed that the average score was significantly lower among women with undetectable viral load (difference = −6.7; 95% CI, −11.2 to −2.1; $P = .004$), higher among those with malnutrition compared with obese women (difference = 15.1; 95% CI, 3.7–26.6; $P = .01$), higher among those who initiated cotrimoxazole before or at study entry (difference = 4.8; 95% CI, .4–9.2; $P = .03$), and higher among women who had twins (difference = 20.5; 95% CI, −0.2 to 41.2; $P = .052$) (see Table 3).

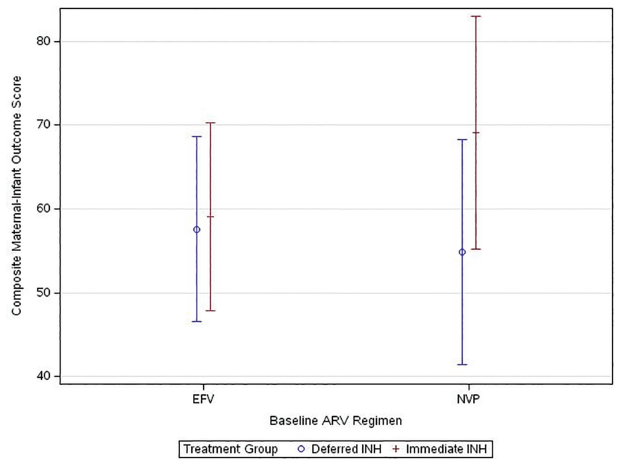

Figure 1. Fitted adjusted least-squares means for maternal–infant composite outcome score according to treatment group and ARV regimen (outcomes displayed for women with undetectable viral load, malnourished, initiated cotrimoxazole before or at study entry, and had a singleton birth). Abbreviations: ARV, antiretroviral; EFV, efavirenz; INH, isoniazid; NVP, nevirapine.

DISCUSSION

Using a novel maternal–infant scoring system has proven to be a useful tool for comparing and understanding the overall risk–benefit of initiating IPT antepartum versus postpartum. In previously reported separate analyses of data from the TB APPRISE trial [19], mother–infant pairs in the immediate INH treatment group had a higher observed percentage of maternal grade 3 or 4 AEs (30.2% vs 28.4%) and infant grade 3 or 4 AEs (47.9% vs 41.4%) compared with those randomized to the deferred INH treatment group. Pairs in the immediate INH arm had a lower observed percentage of maternal deaths (0.4% vs 0.6%), infant deaths (2.5% vs 3.7%), and infant TB (0% vs 0.2%). Both arms had the same observed percentage of maternal TB events (0.6%). No significant differences between treatment groups were seen for any of these outcomes. However, the data suggested a significantly higher proportion of adverse pregnancy outcomes occurring in the immediate INH group (23.6% vs 17.0%; $P = .01$). These results made it difficult to make a risk–benefit comparison of the 2 prevention strategies when analyses are based on individual study outcomes. Since a very small percentage of the study participants experienced the efficacy outcome (incident TB in mothers and in infants) with similar incidence in both study arms, the overall risk–benefit difference was primarily driven by differences in the overall safety profiles of the 2 approaches. Acknowledging that TPT in pregnancy or postpartum effectively decreases TB incidence among women with HIV in TB-endemic regions, the comparison of the risk–benefit of initiating TPT at antepartum versus postpartum is reduced to the question of which TPT initiation strategy is safer.

We did not find a significant overall difference in the composite maternal–fetal/infant scores between the groups who initiated TPT during antepartum versus postpartum, with only a slightly higher mean score (corresponding to lower desirability)

observed among mother–infant pairs in the antepartum TPT arm. However, we detected a significant modifying effect of the maternal ARV regimen. This complements recently reported additional findings on targeted outcomes, such as adverse pregnancy outcomes [22] and maternal hepatotoxicity [23], from analyses of the TB APPRISE trial data. While the use of the composite maternal–fetal/infant outcome does not supplant the need for separate evaluation of maternal, pregnancy, and infant outcomes or, further, by whether they measure safety and efficacy, as illustrated in this work, it does, however, provide important additional insight into the overall benefit of a regimen.

This analysis of the TB APPRISE data also revealed important predictors of the overall well-being of the mother–infant pair as reflected by the composite score. As expected, having detectable viral load at study entry, malnutrition, and twin pregnancy were associated with worse outcomes. Cotrimoxazole use before or at study entry was also associated with worse outcomes. Supplementary Table 5 provides more detailed data comparing the distribution of composite maternal–infant outcomes by these characteristics.

The results of the Delphi process provide insight into stakeholder beliefs about trade-offs between mothers and their fetus/infants and TB and AEs in the context of a prevention study. In particular, it was observed that any negative outcome resulted in a large increment in median assigned score (ie, at least 60 points). Composite outcomes that included death in either the mother or child coupled with any AE in the other had the highest median score followed closely by when one died and the other had no negative event. The large increase in score with negative outcomes suggests that, in a prevention study, which is performed in otherwise healthy persons, preventing AEs is paramount. The following observations were also noteworthy: (1) severe adverse or adverse pregnancy outcomes were generally considered worse than grade 3 or grade 4 AEs in either the mother or child; (2) when events were comparable between mothers and fetus/child they were considered exchangeable, suggesting the equality of both parties with respect to outcomes; and (3) experiencing TB was similar in undesirability as a nonsevere adverse pregnancy outcome.

We have proposed and implemented a rigorous and scientific process for developing composite maternal–infant outcomes that engaged multiple stakeholders with expertise and/or experience in assessing desirability of patient outcomes. A novel feature of this methodology was the utilization of factor analysis, which reduced the number of combinations of maternal–infant paired events that needed to be scored by stakeholders for the second-stage Delphi survey from $4 \times 10 = 40$ to 19 paired events. This not only decreased the burden of survey participation due to what would have been a much larger number of items that each stakeholder would be assigned to score but it may have also alleviated potential measurement errors (ie, incorrect entry of scores) as well as improved internal consistency in the scores assigned by the Delphi panel. Inasmuch as we have involved many stakeholders (clinicians, epidemiologists, other researchers, community advisory members) in the construction of the composite scoring system, the final product may inadequately represent patient preferences. Modification of the score development process to allow the inclusion of pregnant women who are at risk of TB and who would be candidates for TPT may improve the patient-centeredness of the composite outcome. We are proposing to use discrete choice experiments methodology in future research [24], which simplifies ranking composite outcomes by considering scenarios two at a time.

Finally, with regard to TPT among women living with HIV in high-TB-burden regions worldwide, this study highlights the need to consider the HIV treatment regimen during pregnancy in making decisions on whether to initiate TPT during pregnancy or delay initiation to the postpartum period, as the stakeholder weighs the benefits versus the risks for the mother–infant pair. In particular, for women taking an NVP-containing regimen, deferring IPT to the postpartum period is better for the overall well-being of the mother and her infant. With current and future ARV regimens, such considerations should be a key component of TB-prevention research.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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