R21 Specific Aims Example

This preliminary work from an R21 (smaller) grant builds the foundation for an R01 (larger) grant.

Specific Aim 1: To determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit.

1(a): To estimate the prevalence of CT and NG in HIV-infected pregnant women attending their first antenatal visit in Tshwane District, South Africa

1(b): To examine correlates of prevalent CT and/or NG infection and CT/NG treatment outcomes among pregnant women in the study

1(c): To determine the proportion of eligible women consenting to testing (acceptability) and receiving treatment (feasibility)

Specific Aim 1(c) was not part of the original proposal. We added it in response to reviewer feedback.

Specific Aim 2: To describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG in their first antenatal care visit.

2(a): To estimate the frequency of adverse birth outcomes such as premature rupture of membranes, preterm labor or delivery, and small for gestational age, and their association with CT and NG screening and treatment

2(b): To estimate the frequency of HIV MTCT and its association with CT and NG screening and treatment

R01 Specific Aims: FIRST Draft (next two pages)

See how Specific Aim 1 builds upon Aim 1 from the R21 proposal:

"To determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit."

Specific Aim 1: Evaluate scalable interventions to decrease the burden of sexually transmitted infections among pregnant women. Rationale: The WHO currently recommends the syndromic management approach to STI screening and treatment during pregnancy in resource constrained settings. However, work by our group an others has shown that >60% of STI infections among pregnant women are asymptomatic, resulting in the majority of STI during pregnancy remaining unidentified and untreated. To decrease the burden of STIs among pregnant women, scalable interventions to identify and treat STIs during pregnancy are needed. Hypothesis: Diagnostic screening will be associated with a >50% decrease of prevalent STIs at ToD compared to syndromic management, and will result in 50% less over-treatment compared to presumptive treatment of all women. Approach: A four-arm (1:1:1:1), multi-site randomized trial will be conducted. Intervention arms will include 1) diagnostic screening for CT, NG and TV at first ANC, with test-of-cure three weeks post-treatment; 2) diagnostic screening for CT, NG and TV at every clinic visit, with no test-of-cure follow-up; 3) presumptive treatment for CT, NG and TV for all pregnant women. The control group will receive syndromic management, the standard of care in South Africa. Prevalence of CT, NG and TV at ToD will be assessed per intervention arm.

See how Specific Aim 2 builds upon Aim 2 from the R21 proposal:

"To describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG in their first antenatal care visit."

Specific Aim 2: Describe longitudinal birth and infant outcomes for women screened and/or treated for STIs during pregnancy. Rationale: Untreated CT, NG and TV infections during pregnancy are associated with a number of adverse birth outcomes.[8–19] Hypothesis: Diagnostic screening, with appropriate treatment, will be associated with a >20% decrease in the frequency of adverse pregnancy and birth outcomes, compared to syndromic management (control group) or once-off presumptive treatment. Approach: Pregnancy and birth outcomes will be abstracted from maternity case records and labor ward discharge summaries. Frequency of adverse pregnancy and birth outcomes, and their association with diagnostic screening and treatment interventions.

Specific Aim 3: Evaluate the cost per pregnant women screened and/or treated, and the cost-effectiveness per STI averted at time of delivery. Rationale: Evidence on the cost and cost-effectiveness of interventions to decrease the burden of STIs during pregnancy and their impact on adverse birth outcomes is needed by policy makers to determine and evaluate the best use and allocation of scarce resources. Hypothesis : Diagnostic screening, with targeted treatment, for STIs will decrease the prevalence of STIs at ToD, and cost-effectively avert adverse birth outcomes compared to standard practice. *I actually think that presumptive treatment will be the lowest cost option to decrease STIs at time-of-delivery, but that diagnostic screening with targeted treatment will be the most cost-effective intervention. Issues around antibiotic stewardship makes me wary about presumptive treatment. Can we build into the model potential future costs associated with the emergence of drug resistance? I would assume that emergence of drug resistance would be huge cost to pay, and thus decrease the interest in wide scale implementation of presumptive treatment. Plus, we have no idea of the impact of presumptive treatment on the microbiome of the women or infants.* Approach: We will estimate incremental costs and cost-effectiveness of alternative STI screening and treatment interventions among pregnancy women relative to standard practice. Micro-costing studies will evaluate costs incurred and costs averted. Mathematical models will estimate impact on STI prevalence at time of delivery, adverse birth and infant outcomes and DALYs, using proportion diagnostically screened for STIs.

This yellow highlighted text are my own comments and reflections.

At this stage in the process, it is very common to have questions or to be unsure about the exact aims.

R01 Specific Aims: SECOND Draft (next two pages)

Red highlights shows major changes between the first and second drafts.
Yellow comments show my comments/reflections/questions

Specific Aim 1: Evaluate scalable interventions to decrease the burden of sexually transmitted infections among pregnant women. Rationale: WHO currently recommends syndromic management of STIs in resource constrained settings. However, the majority of STIs among pregnant women are asymptomatic, and are thus unidentified and untreated. Hypothesis 1 (H1): Diagnostic screening for CT/NG/TV will be associated with a significant decrease of prevalent STIs at ToD compared to syndromic management, and will result in significantly

Specific Aim 1 now includes measures of costs/cost-effectiveness, which was previously Specific Aim 3

less over-treatment compared to presumptive treatment. H2: Diagnostic screening, with targeted treatment, will cost-effectively avert adverse pregnancy and birth outcomes compared to standard practice. Approach: A four-arm, multi-site randomized control trial will be conducted. Intervention arms will include: 1) diagnostic screening and targeted treatment at first ANC, with test-of-cure (ToC) follow-up; 2) diagnostic screening and targeted treatment at specified clinic visits, no ToC follow-up; 3) universal presumptive treatment for CT/NG/TV; 4) syndromic management (control group). Outcomes: Prevalence of CT/NG/TV at ToD per intervention arm. Incremental costs and cost-effectiveness of different interventions among pregnancy women relative to standard practice. Micro-costing studies will evaluate costs incurred and costs averted.

This new specific aim has been added to focus on the vaginal microbiome

Specific Aim 2: Describe changes in the composition and structure of the vaginal microbiome in response to targeted and presumptive antibiotic treatment for STIs. Rationale: Perturbations to the vaginal microbiome following presumptive or targeted treatment, as assessed by high-throughput sequencing, have not yet been carefully documented. Such data is needed to understand treatment failure rates, and what impact these perturbations may have on pregnancy and birth outcomes. Hypothesis: *I'm still thinking about the most appropriate hypothesis*. Approach: We will longitudinally collect vaginal specimens (i.e., before and after presumptive/targeted antibiotic treatment, at ToC, and periodically during pregnancy) from HIV-infected and uninfected women. The composition and structure of the vaginal microbiome will be assessed as a function of HIV and STI status, and antibiotic treatment regimen received.

Longitudinal outcomes are now in Specific Aim 3 instead of Aim 2, and the aim was adjusted to reflect the new Aim 2 focus on the vaginal microbiome

Specific Aim 3: Describe longitudinal pregnancy and birth outcomes as a function of screening/treatment interventions and the structure and composition of the vaginal microbiome. Rationale: Untreated CT, NG and TV infections during pregnancy are associated with adverse birth outcomes.[8–19] Hypothesis: Diagnostic screening, with targeted treatment, will be associated with a >20% decrease in the frequency of adverse pregnancy and birth outcomes, compared to syndromic management (control group) or once-off presumptive treatment. Approach: Pregnancy and birth outcomes will be abstracted from maternity case records and labor ward discharge summaries. We will assess the frequency and type of adverse outcomes, and their association with intervention arms.
I still need to flesh out the rationale, hypothesis and approach for Aim 3.

R01 Specific Aims: THIRD Draft

Red highlights shows major changes between the second and third drafts

Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women. Hypothesis 1 (H1): Compared to syndromic management, diagnostic screening with TT will significantly decrease prevalent STIs at time of delivery and reduce adverse pregnancy/birth outcomes. H2: Compared to single, point-in-time screening at 1st ANC with TT and ToC, periodic repeated diagnostic screening will decrease incident STIs at time of delivery. Approach: A three-arm RCT will be conducted; Arm 1) diagnostic screening + TT at first ANC, with ToC follow-up; Arm 2) periodic diagnostic screening throughout ANC with TT, no ToC follow-up; Arm 3) syndromic management (standard-of-care). Prevalence and incidence of STIs at time of delivery, and frequency and type of adverse pregnancy/birth outcomes per intervention arm will be assessed.

Language in the Aim is more specific and precise about what will be done

Four-arm RCT switched to three-arm (removed universal presumptive treatment arm)

Aim 2: Evaluate the cost per pregnant woman diagnostically screened, and the cost-effectiveness per STI averted at time of delivery and adverse birth outcome. Hypothesis 1 (H1): Compared to syndromic management, diagnostic STI screening, with TT, will cost-effectively avert STIs at time of delivery, and reduce adverse pregnancy and birth outcomes. Approach: We will estimate incremental costs and cost-effectiveness of alternative STI screening interventions relative to standard practice. Micro-costing will evaluate costs incurred and costs averted. Mathematical modeling will estimate impact on STI prevalence at time of delivery, adverse pregnancy/birth outcomes and DALYs, using proportion diagnostically screened for STIs.

Added cost-effectiveness back in as its own Aim

Aim 3: Investigate the relationship between the vaginal microbiome and STI treatment outcomes. Hypothesis: Non-*Lactobacillus* dominant vaginal CST will be associated with CT and TV treatment failures. Approach: Vaginal specimens will be collected at all ANC and ToC clinic visit. Vaginal bacterial communities will be analyzed by Illumina sequencing; DADA2 software will infer exact amplicon variants. CT and TV treatment outcomes will be assessed as a function of the composition and structure of associated vaginal microbiomes.

Aim 3 collapses the previous Aim 2 and Aim 3 together to be more succinct.

"Rationale" subsections were cut from all Aims.

R01 Specific Aims: FOURTH Draft – 1st TRY SUBMISSION

Red highlights shows major changes between the third and fourth drafts

Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women. Hypothesis 1 (H1): Compared to syndromic management, diagnostic screening with TT will significantly reduce adverse pregnancy/birth outcomes and decrease prevalent STIs at time of delivery. H2: Compared to single, point-in-time screening at 1st ANC with TT and ToC, periodic repeated diagnostic screening will decrease incident STIs at time of delivery. Approach: A hybrid type 1 effectiveness-implementation design three-arm randomized controlled trial will be conducted; Arm 1) diagnostic screening + TT at first ANC, with ToC follow-up; Arm 2) periodic diagnostic screening throughout ANC with TT, no ToC follow-up; Arm 3) syndromic management (standard of care). Prevalence and incidence of STIs at time of delivery, and frequency and type of adverse pregnancy/birth outcomes per intervention arm will be assessed.

Swapped order of outcomes and STIs

More details on the type of RCT

Aim 2: Evaluate cost per pregnant woman diagnostically screened and treated, cost of adverse pregnancy and birth outcomes, and cost-effectiveness per STI and DALY averted. H1: Compared to syndromic management, diagnostic STI screening + TT will cost-effectively avert STIs at time of delivery, and reduce adverse pregnancy and birth outcomes. Approach: We will estimate the costs of alternative STI screening interventions relative to standard practice as well as the costs of managing adverse pregnancy/birth outcomes. Decision analytic modeling will estimate the cost-effectiveness per STI and DALY averted.

Major refinement of language

Aim 3. Investigate the relationship between the vaginal microbiome and CT treatment failure in pregnant women. H1: Chlamydia-infected pregnant women with BV-associated vaginal microbiota CSTs will be significantly more likely to have clinical treatment failure as identified at ToC. Approach: We will conduct a nested case-control (1:2) study using vaginal specimens collected from CT-infected women at first ANC, 1 and 2 weeks post-treatment and then at ToC (3 weeks post-treatment).

Focus specifically on CT treatment failure instead of "STI treatment outcomes", which required changing the whole hypothesis for this Aim

Reviewer Feedback & Our Response : 1st Submission

Impact Score:27 Percentile:15

RESUME AND SUMMARY OF DISCUSSION: In this application, the Principal Investigator proposes to establish a trial to assess the impact and cost-effectiveness of different diagnostic and screening strategies to decrease the burden of sexually transmitted infections (STIs) in pregnant women. STIs are common globally and have been associated with adverse birth outcomes. The reviewers agreed that the proposed studies are highly significant due to the impact and burden of STIs on birth outcomes in sub-Saharan Africa. The studies were deemed highly innovative as they examine the role of the microbiome on STI treatment outcomes as well as assess means to improve both cost-effectiveness and birth outcomes. Major strengths of the application were the focus on implementation to inform policy on STI testing strategies as well as cost assessment, the well-designed study, and strong investigative team. Enthusiasm was slightly dampened by the concern that syndromic management will impact STI detection since, based on the preliminary data by the investigative team, there is a high rate of asymptomatic infection. Nevertheless, the panel agreed that the proposed studies are highly significant and can potentially have a high overall impact on the management of STIs.

Reviewer comment 6: "My enthusiasm is dampened [by] …concern about…a standard of care arm…given that most STIs are asymptomatic" and "…equipoise"

Response 6: Syndromic management is the standard of care in all low and middle-income countries. Demonstrating the impact/cost effectiveness of STI screening v. standard of care with respect to adverse birth outcomes is critical to produce high-level evidence to inform policy change.

R01 Specific Aims: 2nd TRY RESUBMISSION

No changes!

Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women. Hypothesis 1 (H1): Compared to syndromic management, diagnostic screening with TT will significantly reduce adverse pregnancy/birth outcomes and decrease prevalent STIs at time of delivery. H2: Compared to single, point-in-time screening at 1st ANC with TT and ToC, periodic repeated diagnostic screening will decrease incident STIs at time of delivery. Approach: A hybrid type 1 effectiveness-implementation design three-arm randomized controlled trial will be conducted; Arm 1) diagnostic screening + TT at first ANC, with ToC follow-up; Arm 2) periodic diagnostic screening throughout ANC with TT, no ToC follow-up; Arm 3) syndromic management (standard of care). Prevalence and incidence of STIs at time of delivery, and frequency and type of adverse pregnancy/birth outcomes per intervention arm will be assessed.

Aim 2: Evaluate cost per pregnant woman diagnostically screened and treated, cost of adverse pregnancy and birth outcomes, and cost-effectiveness per STI and DALY averted. H1: Compared to syndromic management, diagnostic STI screening + TT will cost-effectively avert STIs at time of delivery, and reduce adverse pregnancy and birth outcomes. Approach: We will estimate the costs of alternative STI screening interventions relative to standard practice as well as the costs of managing adverse pregnancy/birth outcomes. Decision analytic modeling will estimate the cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and CT treatment failure in pregnant women. H1: Chlamydia-infected pregnant women with BV-associated vaginal microbiota CSTs will be significantly more likely to have clinical treatment failure as identified at ToC. Approach: We will conduct a nested case-control (1:2) study using vaginal specimens collected from CT-infected women at first ANC, 1 and 2 weeks post-treatment and then at ToC (3 weeks post-treatment).

Reviewer Feedback: 2nd Submission

Impact Score:33 Percentile:21

REVIEWER 3:

This revision responds to many initial reviewer concerns, providing solid explanation on why HIV+ and HIV- women are included as well as sample size justification, addition of DSMB, PI effort, updating enrollment table, etc. Preliminary data supporting Aim 3 regarding the mechanism have been added, as well as data on the relationship between BV and chlamydial organism load. It remains unclear in this proposed study whether these pregnant women with symptomatic BV will be treated, as clinical guidelines suggest they should be. Previous Reviewer 2 indicates persistent infection and treatment failure are not distinguished, and this remains unclear. For example, what proportion of the not-cleared infections at test of cure occurs *in the absence of* non-adherence/partner re-exposure? As only 55% of women provided male partners with treatment, and adherence in male partners is unknown. Regarding concern about overlapping roles of investigators, this is mostly addressed but there is still some lack of clarity on the roles of biostatisticians. Overall, the investigative team is excellent, the environment is strong, and the goal to reduce adverse birth outcomes through STI testing and treatment is of public health and clinical relevance, and the aim to determine impact of vaginal microbiome on chlamydia treatment outcome is innovative. However, the trial methodology is not innovative, and the potential magnitude of the impact of VMB on CT treatment outcome is uncertain.

R01 Specific Aims: 3rd TRY, NEW SUBMISSION

Red highlights shows major changes between the second and third submission

Aim 1: Evaluate different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes. Hypothesis 1 (H1): Compared to syndromic management, diagnostic STI screening and treatment will significantly reduce adverse birth outcomes. H2: Compared to a single diagnostic screening with follow-up test-of-cure (ToC), repeated screening and treatment (no ToC) will significantly decrease STIs at delivery. Approach: A three-arm randomized controlled hybrid-effectiveness trial will be conducted; Arm 1) diagnostic screening and treatment at first ANC + ToC follow-up; Arm 2) repeated screening and treatment throughout ANC (no ToC); Arm 3) syndromic management (control). Prevalence and incidence of CT, NG and TV at delivery and frequency of adverse birth outcomes by study arm will be assessed.

Wording changed for flow and refinement

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and DALY averted. H1: Compared to syndromic management, STI diagnostic screening will cost-effectively avert STIs at delivery, and reduce adverse birth outcomes. Approach: We will estimate the comparative costs of different STI screening strategies relative to standard practice as well as the costs of managing adverse birth

Aim 2 only focuses on cost of adverse birth outcomes, not adverse pregnancy

outcomes. Decision analytic modeling will estimate the cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women. H1: CT-infected pregnant women with BV-associated vaginal microbiota CSTs will be significantly more likely to have persistent infections at test-of-cure compared to women with non-BV associated CSTs. Approach: A nested case-control (1:2) study using vaginal specimens collected from CT-infected women at first ANC, 1, 2 and 3 weeks post-treatment.

Aim 3 now focuses on persistent infections rather than CT treatment failure.

Generally tightened up language for all Aims

Reviewer Feedback: 3rd Submission

Impact Score:43 Percentile:25

OVERALL:

deemed highly significant with a strong scientific premise as it is testing two screening strategies due to the high incidence of asymptomatic STIs among women with and without HIV. Major strengths of this well-written application include the extensive preliminary data, the incorporation of cost-effectiveness analysis, as well as the very high subject retention rate. Enthusiasm was lowered by several weaknesses. The reviewers raised some concerns on the STI testing result interpretation, the handling and analysis of the data collected, as well as the lack of clarity on male partner role. Furthermore, the reviewers questioned, give the teams preliminary data, whether the syndromic management arm is necessary. Overall, this is a well written application that has the potential to inform standard of care. However, the panel agreed that the weaknesses raised mostly in the experimental approach lowered overall impact to moderate.

REVIEWER 3:

burden of CT/NG/TV among pregnant women and reduce adverse birth outcomes. Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and DALY averted. Aim 3: Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women. The investigator team is strong, the study design is innovative, and the environment is supportive however my enthusiasm is tempered by the use of a syndromic approach arm in this study given the both the preliminary data from this team and data from other studies which clearly demonstrate inferiority of this approach.

REVIEWER 4:

- The study did not set an upper limit gestational age for enrollment however it does not discuss how women presenting at or after 31weeks and randomized to arm 2 will be managed and how their data will be utilized in the analysis
- Do not think that the syndromic management arm is necessary given the preliminary data (HPTN 040) and data from other studies clearly show increased MTCT of HIV in the presence of maternal STI as well as historical data on the fetal and neonatal complications of STI (the are rates of transmission and complications available that can be used as inputs into costing – a publicly available dataset is not necessary for this). Why not utilize historical data on transmission of STIs and subsequent infant morbidity/mortality in the costing analysis to provide an estimate of the cost of adverse outcomes?

R01 Specific Aims: 4th TRY, RESUBMISSION

Red highlights shows major changes between the third and fourth submission

Instead of comparing to syndromic management, H1 compares to a one-time diagnostic test to repeat testing

Aim 1: Evaluate three different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes. Hypothesis 1 (H1): Compared to a one-time diagnostic test for STIs at a woman's first ANC visit, repeat testing algorithms will significantly reduce adverse birth outcomes. H2: Compared to diagnostic screening with follow-up test-of-cure (ToC), repeat screening and treatment without any ToC will significantly decrease STIs at delivery. Approach: A three-arm randomized controlled hybrid-effectiveness trial will be conducted; **Arm 1**) diagnostic screening and treatment at first ANC + ToC follow-up; **Arm 2**) repeat screening and treatment throughout ANC (no ToC); **Arm 3**) one-time diagnostic screening and treatment at first ANC, no ToC (control). Prevalence and incidence of CT, NG and TV at delivery and frequency of adverse birth outcomes by study arm will be assessed.

Aim 2 is updated to reflect same changes in Aim 1

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and disability-adjusted life-year (DALY) averted. H1: Compared to one-time diagnostic screening and treatment at first ANC, diagnostic screening with follow-up ToC and repeated screening with treatment (no ToC) will be more cost-effective to avert STIs at delivery, and reduce adverse birth outcomes. Approach: We will estimate and compare the costs of different STI screening strategies relative to control, and the costs of managing adverse birth outcomes. Decision analytic modeling will estimate the cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women. H1: CT-infected pregnant women with BV-associated vaginal microbiota CSTs will be significantly more likely to have persistent infections at test-of-cure compared to women with non-BV associated CSTs. Approach: A nested case-control (1:2) study using vaginal specimens collected from CT-infected women at first ANC, 1, 2 and 3 weeks post-treatment.

FUNDED! **Impact Score:27** **Percentile:10**