COVER PAGE PROTOCOL DETAILS

Protocol Title: Our Family Our Future: A Resilience-oriented Family Intervention to Prevent Adolescent HIV/STI Infection and Depression in South Africa

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A. PURPOSE OF STUDY

The objective of this study is to assess the efficacy of a family-based preventive intervention designed to reduce sexual risk behaviors linked to HIV/STI acquisition or transmission, and depressive symptoms among South African adolescents (14-16 years). We have three specific aims. First, we test the efficacy of the *Our Family Our Future* intervention in preventing HIV/STI acquisition among adolescents (ages 14-16) by reducing HIV/STI risk behavior, and preventing onset of clinical depression by randomizing N=880 adolescents (and their parents) to *Our Family Our Future* intervention or usual care with 6- and 12-month outcome assessments. Our hypothesis is that adolescents randomized to *Our Family Our Future* will show lower incidence of composite HIV/STIs, lower rates of sexual risk behavior, and a greater reduction of depressive symptoms than adolescents in the usual care condition. Second, in an analytical aim, we examine the extent to which the impact of the *Our Family Our Future* intervention is mediated by changes in resilience; behavioral skills and efficacy; norms and attitudes relating to sex, condom use, gender; and family interactions relevant to prevention and moderated by the effect of sociodemographics; structural disparities; severity of parental depression; family HIV; and social protections. Third, we identify barriers and facilitators to implementing *Our Family Our Future* within a community-based organization setting to provide data for future dissemination using fidelity data to examine intervention delivery quality and qualitative interviews (N=30-45 interviews) from adolescents, families, and stakeholders to understand the experience of the intervention.

The intervention being tested in this study - *Our Family Our Future* - was developed through the integration and adaptation of two existing empirically supported family-based models for preventing HIV risk behaviors (*Keepin' It Real*) and depression (*Family Talk*). *Keepin' It Real* was named as a best-evidence HIV preventive intervention by the US Centers for Disease and Control and Prevention (CDC); *Family Talk* was named as a best-evidence depression preventive intervention by the US Substance Abuse and Mental Health Services Administration (SAMHSA). These organizations rank "best-evidence" interventions as interventions that have documented positive effects on primary targeted outcomes in peer-reviewed journals (multiple quasi-randomized and randomized controlled trials) and documented evidence of implementation with multiple populations and settings. The two interventions chosen have shown efficacy in multiple populations and settings including international (although not in South Africa) and U.S. based populations with similarities with the South African context (high mental health or HIV risk, low-income, inner-city, community contexts, non-clinician delivery). The original interventions emphasize family strength and resilience. The original interventions use similar techniques to improve mood and sexual safety, have similar theorized mechanisms of change (cognitive behavioral theory) and common key elements (family bonding, functioning, problem solving, communication; positive parenting; self-efficacy; behavioral skills) and thus, are appropriate for integration and delivery simultaneously in one adapted intervention. Integration and adaptation of the two existing empirically supported models into one combined model (tested in this trial, and called *Our Family Our Future*) is purposeful given the reinforcing effects of depression on adolescent sexual risk behavior. Original intervention designers helped us identify and retain core behavioral change components in the final integrated and adapted intervention - *Our Family Our Future* - being tested in this study.

Our Family Our Future is a 'selective' prevention program, designed to address HIV/STI acquisition, sexual risk behavior, and depression among adolescents (ages 14-16) in communities with high HIV prevalence and from families where adolescents exhibit mild, potentially

troublesome, depressive symptoms but do not reach the threshold for further screening for a significant clinical depressive disorder. This intervention involves parent-child dyads who receive the intervention in a community setting, in a facilitated group format. The intervention is comprised of 3-hour sessions, held weekly for 3 consecutive weeks with an individual family meetings in the third or fourth week depending on family desires. The intervention also includes take-home activities to deepen behavioral engagement with the week's received session and to "prime the pump" for the upcoming week's session. The final intervention covers the following topics in combined adolescent-parent sessions using role play, group activities, discussion and debate, and facilitation: 1) family needs and values; 2) community strengths and challenges; 3) communication skills; 4) talking about sensitive topics – HIV, STIs, sex, puberty, mental health, and discipline; 5) HIV and STI transmission, prevention, and living with HIV; 6) healthy individual and family coping with mental distress, adolescent sexual health, and other challenges; and 7) family goals and strategies for healthy interactions and problem-solving. There are also separate adolescent and parent sessions. For adolescents, topics include: 1) peer influences; 2) healthy relationships and gender roles and interpersonal violence; 3) sexual decision making and communication; 4) condom use and contraception; and 5) consequences of sexual decisions. For parents, these include: 1) adolescent development and reproductive health; 2) healthy relationships and gender roles; 3) psychoeducation on depression; 4) communicating about sexual and mental health; and 5) condom use and contraception.

B. Study Aims, Background, and Significance

Study Aims

Adolescents and young people account for the majority of new HIV infections in South Africa, a country at the epicenter of the epidemic with the largest share (16%) of all new global infections.[1-5] A sub-set of adolescents with depression are at disproportionate risk for acquisition of sexually transmitted infections (STIs) such as HIV. These adolescents are more likely to be from families with depression given biological and environmental factors linked to family depression.[6-9] In these families, family communication and functioning – elements of protective family environments for adolescents prevention – are adversely affected. In South Africa, adolescents and parents at elevated risk for depression are likely to live in communities affected by social and structural disparities such as poverty and violence, and where HIV prevalence and incidence is high.[10-17] In addition to altered family environments that impact adolescent risk, adolescents with depression experience emotional dysregulation that may affect accurate appraisals of risk, and are more likely to engage in substance use to avoid or numb distressing emotions, further diminishing implementation of HIV/STI prevention behaviors. Engaging adolescents (ages 14-16) in integrated prevention of HIV/STIs-depression offers unique opportunities to habituate life-long protective behaviors. In South Africa, this age represents a critical epidemiological transition with HIV incidence increasing 6-fold, from 0.25% among 2-14 year olds to 1.49% among 15-24 year olds.[2] Similarly, the age of 14-16 years corresponds to elevated risk for depression onset.[18-20] Engaging families in prevention is age- and developmentally-appropriate for adolescents. There is a current gap in knowledge, with no existing efficacious interventions in South Africa that integrate prevention of adolescent HIV/STIs

with depression in community settings. We urgently need to expand our toolbox for adolescent prevention by including families. To ensure responsiveness in South Africa, interventions need to be designed for the setting including high HIV prevalence, poverty, low literacy, culture, and language.

The long-term goal of this study is to promote adolescent health resilience in a global priority population and setting by expanding our prevention toolbox through age- and developmentally-tailored interventions to prevent adolescent HIV, STIs, and depression. The overall objective of this study is to test the efficacy of Our Family Our Future, an intervention integrating prevention of HIV/STI-depression among adolescents (ages 14-16) that substantively includes families for maximum prevention benefit. This is a 'selective' prevention approach, focusing on communities with high HIV prevalence and adolescents reporting mild, but worrisome depressive symptoms. Our rationale for this efficacy trial is to build off the outstanding acceptability and feasibility findings from the randomized pilot trial of Our Family Our Future (detailed in Background below). We propose three specific aims:

1. **Test the efficacy of the *Our Family Our Future* intervention in preventing HIV/STI acquisition among adolescents (ages 14-16) by reducing HIV/STI risk behavior, and preventing onset of clinical depression by randomizing N=880 adolescents to *Our Family Our Future* intervention or usual care with 6- and 12-month outcome assessments.** Our working hypothesis is that adolescents randomized to *Our Family Our Future* will show lower incidence of composite HIV/STIs, lower rates of sexual risk behavior (e.g.., lower number of unprotected sex acts), and a greater reduction of depressive symptoms than adolescents in the usual care condition.
2. **Examine the extent to which the impact of the *Our Family Our Future* intervention is (a) mediated by changes in resilience; behavioral skills and efficacy (e.g., condom use, sex refusal); norms and attitudes relating to sex, condom use, gender; and family interactions relevant to prevention (e.g., communication, functioning) and (b) moderated by the effect of sociodemographics; structural disparities (e.g., food insecurity); severity of parental depression; family HIV; and social protections (e.g., government grants).**
3. **Identify barriers and facilitators to implementing *Our Family Our Future* within a community-based organization setting to provide data for future dissemination (presuming *Our Family Our Future* is efficacious).** We examine processes critical to future dissemination through (a) fidelity data examining adherence to core active components of the standardized intervention manual guiding consistent delivery of the intervention; and (b) qualitative data on the experience during and post-implementation from adolescents, families, and stakeholders using N=30-45 in-depth interviews.

The expected outcomes of this study includes efficacy data for the first integrated family intervention for prevention of adolescent HIV/STIs with depression in a community setting, and data to inform future dissemination, implementation, and scale-up.

BACKGROUND

This study is based off of several preliminary studies. Multiple Principal Investigator (M-PI), Dr. Kuo's early work developed a program of community-engaged formative research documented the sexual, reproductive, and mental health intervention needs of adolescents and their families in South Africa.[21-32] Dr. Kuo, in collaboration with Drs. Stein, Atujuna, Brown, Mathews, and Beardslee, led a study that continued this line of research by testing the

acceptability and feasibility of the Our Family Our Future intervention in formative studies (approved by University of Cape Town's HREC in protocol 072/2013 and sub-study protocol 796/2014). Collectively, these studies cumulatively reflect careful steps for intervention design, as summarized in the ORBIT Model for Developing Behavioral Treatments[33] and other models.[34]

The qualitative study (072/2013) identified aspects of the original interventions where new content needed to be added, altered, or strengthened to ensure response and engagement with the target population. We added content to address context-specific factors that affect adolescent sexual risk including poverty, gender disparities, interpersonal violence, gang activity, and drug and alcohol use. We adapted original intervention content to better relate to family mental health outcomes and adolescent sexual risk behavior including emphasizing and building on family resilience and future-orientation. We altered intervention content to better capture language (including Xhosa and slang) words for mental health, the adolescents and parents who might already be infected with HIV, sexual partnerships and more; and tailoring content to address unique context-specific beliefs regarding origins, transmission, prevention of HIV. We also identified a need to enhance motivation and behavioral components of the intervention based on findings and supported by a global meta-analysis of effective adolescent HIV preventions.

The randomized pilot trial (HREC protocol 796/2014) of *Our Family Our Future* was conducted with N=146 adolescents and parents (73 family dyads). Randomization achieved balance in arms. We achieved 100% retention at both 1- and 3-month follow-up time-points for all adolescents and parents in our pilot trial. HREC protocol 796/2014 showed outstanding acceptability, feasibility, and direction of effects.[35-45] Our Family Our Future is reaching high-risk adolescents and families. The intervention is reaching distressed families where risk for adolescent depression onset is high. In our pilot, 28% of adolescents met criteria for mild, but concerning depressive symptoms suggesting prevention was needed to arrest further decline. Adolescents from families in distress are at elevated risk for poor health outcomes; in our sample, adolescents were at high risk given 44% of parents met criteria for mild, but concerning depressive symptoms, 35% reported symptom levels corresponding to depression, and 29% were living with HIV. Adolescents – who were on an average age of 14 years, 100% Black African, 100% isiXhosa, 56% female, 44% male – exhibited high HIV and STI risk. At baseline, 69% of adolescents had never tested for HIV and 92% had never tested for other STIs despite living in a community with high rates of HIV and STIs. A significant number of adolescents (13-15 years) had started their sexual lives: 25% reported vaginal or anal sex. Sexual risk behavior was high: 25% reported perpetrating forced or coercive oral sex, sexual touching, and/or penetrative sex.[38] Among adolescent who engaged in penetrative sex, 30% reported sexual partners of unknown HIV status, 36% had 5+ partners, 31% had recent unprotected sex, and 31% engaged in inconsistent condom use. Our pilot indicated a need to shift our target age range to 14-16 years in this efficacy study to capture greater proportions of adolescents with depressive symptoms and engaged in HIV/STI risk behavior. This slight age adjustment offers an optimal scientific target for 'selective' prevention while retaining the salience of our family approach.

Our Family Our Future is highly feasible and can be implemented with rigorous fidelity. We conducted a randomized pilot trial with N=146 adolescents and parents (73 family dyads) with scientific rigor. Randomization achieved balance in arms with no significant differences between groups in regards to key variables. We also achieved 100% retention at both 1- and 3-month follow-up time points for all adolescents and parents in our pilot trial in spite of a challenging scientific environment including working in the community in house-to-house recruitment, tracking, and tracing with no street names, lack of home addresses, no postal service, few landline phones, and frequent seasonal migration. Based on fidelity observation by a neutral observer for

20% of sessions, intervention facilitators showed skilled delivery with an average ranking of “3” - the highest ranking on a 1 to 3 scale equivalent to demonstrated skills >75% of the time for active engagement with participants; active listening; respectful, positive communication; guided discovery; warmth, concern, confidence, professionalism; empowerment of families; building participant confidence; maintenance of appropriate pace of group discussion; ending on a positive note. In addition, guided by a manualized protocol to standardize delivery for core behavioral change components, facilitators received high fidelity rankings with >90% fidelity to core components. We will implement the following strategies to improve existing outstanding feasibility in this efficacy study: To increase efficiency and feasibility of recruitment as we transition from a pilot to this large-scale trial, we will target recruitment at Masiphumele, a well-respected and established community center run by DTHF to supplement our previous house-to-house strategy. This targeted recruitment will increase efficiency given concentrated presence of adolescents that are present at the center, and it’s location in a community with high HIV/STI prevalence and structural disparities that increase risk for poor mental health. Although sessions, on average, had good attendance, families identified ways to improve acceptability and attendance in satisfaction evaluations and during dissemination feedback including the need to: (1) readjust timing of sessions that occur in the winter season (to address family concerns about sessions ending after dark, a safety concern for families traveling in the high violence community); (2) increase travel reimbursement to cover costs completely; (3) increase food when sessions coincide with lunch and dinner times; (4) provide flexibility in the group composition (groups were previously fixed) to provide greater flexibility for attendance days and times; and (5) shift to an organization whose community site is not affected by gang violence to increase safety and diminish fears of random violence while enroute to the site.

Our Family Our Future is appealing to high-risk adolescents and their families. Overall the program was ranked ‘good’ or ‘excellent’ in quality by 100% of adolescents and parents. 100% of adolescents and parents felt they received desired information. In regards to satisfaction with information, 90.6% of adolescents and 100% of parents felt ‘most’ and ‘all needs were met’. In terms of the intervention helping them to deal effectively with important issues, 100% of adolescents and 96.9% of parents felt it ‘helped’ and ‘helped a great deal’. In terms of intervention meeting overall needs, 100% of adolescents and 96.9% of parents felt they were ‘mostly’ and ‘very satisfied’. 96.9% of adolescents and 93.5% of parents felt ‘mostly’ and ‘very satisfied’ with the overall intervention. 96.7% of adolescents and 100% of parents as ‘mostly’ and ‘very satisfied’ with facilitators. 100% of participants would recommend the intervention to others and attend again.

Our Family Our Future shows promising direction of behavioral change effects. The primary aim of the pilot study (796/2014) was to investigate feasibility and acceptability; while we were not powered for efficacy (and thus saw no differences in trial arms), we saw promising direction of effects in the intervention arm. Adolescent and parent resilience improved, with adolescent resilience scores (Connor-Davidson Resilience Scale) increasing from 25 points at baseline to 26 points at 3 months; and parents scores increasing from 29 points at baseline to 31 points at 3 months. For depression, we recruited for a sample of adolescents who had depressive symptoms but at levels not yet reaching the threshold for a significant clinical depressive disorder. The intervention arm showed diminished depressive symptoms, with adolescent CESD-C scores decreasing from 12 points (baseline) to 8 points (1-month post intervention) to 7 points (3-months post intervention); and parent CES-D scores from 12 points (baseline) to 11 points (1- and 3-month). Family interactions changed positively: children had increased knowledge and

understanding of parental depressive symptoms; there were stronger parental norms on the importance of adolescents delaying sex until older ages and using condoms if having sex; and there were improved family communication and functioning. HIV risk perception and knowledge increased: adolescent and parent perceptions of adolescent HIV risk susceptibility increased; and adolescent knowledge on causes, modes of transmission, and treatment for HIV improved at 1- and 3-months compared to baseline. Motivations to engage in protective behaviors increased: a larger proportion of adolescents subscribed to attitudes on the pros of delaying sex and a smaller proportion subscribed to attitudes on the cons of delaying sex at 1- and 3-months compared to baseline. Future protective behavior intentions increased, with increased intentions to use condoms at 1- and 3-months compared to baseline. Protective behavior self-efficacy increased, including improved condom use self-efficacy. Protective HIV/STI behavior change occurred: HIV testing increased, with 22% of adolescents newly testing for HIV between baseline and combined 1- and 3-month time points; inconsistent condom use decreased from 4.2% to 2.8%. Moreover, we would have expected engagement in oral, anal, and vaginal sex to stay steady or increase over time due to natural trajectories of sexual activity in this age range. Instead, sexual activity decreased; 19% of the intervention arm engaged in oral, anal, and vaginal sex at baseline but this decreased to 10% at 1-month and 3-months post-intervention.

SIGNIFICANCE

Acquired immunodeficiency syndrome (AIDS) is the leading cause for death among adolescents in Africa, and the second leading cause of death for adolescents worldwide.[46] Adolescents and young people 15-24 years account for 40% of all new human immunodeficiency virus (HIV) infections each year, with the majority in sub-Saharan Africa.[1,3-5] South Africa is at the global epicenter of this HIV crisis, accounting for the largest share of new HIV infections of any country in the world (16% of global total) and the world's largest population of people living with HIV (12.2% prevalence with approximately 1 in 10 South Africans living with HIV).[1,2] Our current toolbox for adolescent prevention needs innovation and expansion in this high priority setting given alarming HIV incidence of 1.5% and behavioral data from a national study indicating 40% of 15-24 year olds did not think they were at risk for HIV, and only 26% able to correctly identify common modalities of HIV transmission and prevention.[2] We urgently need to test the efficacy of age- and developmentally-tailored interventions that engage adolescents and their families, and are appropriate for low-resource settings.

A sub-population of adolescents with psychological distress, especially internalizing disorders such as depression, are uniquely at risk for STIs including HIV and engaging in sexual risk behaviors. Adolescents with depressive symptoms experience emotional dysregulation, linked to inability to control behaviors when emotionally distressed. Maladaptive emotion management responses to alter the duration and/or intensity of emotional experiences[47] such as avoidance and numbing can increase sexual risk behavior by diminishing an individual's awareness of their environment, decreasing sensitivity to cues regarding impending risk,[48] or interfering with the correction of inaccurate appraisals of safety.[49] Individuals may use substances to avoid or numb intense emotions, but this can further increase HIV/STI risk by skewing perceptions of risk, and by interfering with decision-making or implementation of protective behaviors.[50] Although evidence on the relationship between depression and HIV/STI risk is mixed for general populations, there is a clearer relationship in populations related to our target sample.[51-58] Three South African studies (n=1,979; n=1,275; n=645) found a significant

association between depression and greater HIV risk (sex with older partners, transactional sex, unprotected sex, incorrect condom use, forced sex).[52,59,60] A meta-analyses showed depression was twice as likely in HIV-infected individuals (d=0.69).[61] Exposure to stressors is a common risk for depression and trauma; the literature around trauma and HIV risk shows a strong relationship,[62-67] including among African-American adolescents[68-70] and South African populations.[71] Adolescent studies showed those with affective disorders including depression were four times as likely to have multiple sexual partners,[72] and twice as likely to engage in risky sexual intercourse.[73] A systematic review indicated adolescents with poor mental health were more likely to engage in STI risk behaviors compared to same-age peers,[74] possibly due to lower self-efficacy in negotiating safe sex and mediated by factors such as parental and peer influence.[74-76] South African adolescents are uniquely at risk for depression in communities disproportionately affected by HIV due to poverty, structural disparities, orphanhood, and family HIV illness.[10-17] Co-occurrence of HIV/STIs and depression represent a cluster of reinforcing risks that need to be tackled via integrated prevention.

Adolescents (ages 14-16) are ideally suited for integrated HIV/STI-depression prevention. This age marks a developmental transition corresponding to elevated HIV/STI risk as adolescents consider or engage in their first sexual experiences. In a large longitudinal prospective cohort study of South African adolescents, 70% had engaged in sexual foreplay and oral sex by 13 years; the median age of penetrative sexual debut was 15 years, with 14.2% of females and 38.2% of males engaged in penetrative debut at this age.[77] Rates of sexual activity are much higher in our study site, even among younger populations; 30% of 13 year olds engaged in anal, oral, or vaginal sex.[78] Adolescence also corresponds to elevated risk for depression, with rates of depression onset increasing rapidly during early- and mid-adolescence.[18-20] Although adolescents face elevated HIV/STI and depression risks aligned with age- and developmental transitions, adolescence also presents ideal opportunities for prevention that can have long-lasting impacts over the life-course. Preventive interventions can capitalize on the transition into adulthood by tapping into motivations for skill acquisition just as adolescents learn constructive behavioral health patterns. Preventive interventions can tap into motivations for autonomy and creativity just as adolescents acquire independence over their health responsibilities. Because adolescence is a stage of creativity and exploration of new ideas, exposure towards protective behaviors during this life transition can build resilience and lead to habituation of life long prevention behaviors. Interventions emphasizing skill acquisition, identity formation, and prevention should involve parents for this age group. We use the term ‘parents’ to include any adult in the parental role given high rates of orphaning.[79]

Substantively engaging families in integrated prevention of adolescent HIV/STI-depression offers opportunities to deepen the impact of intervention programming. Parents have a strong influence on adolescent motivations, decisions, and behaviors relating to health. In regards to HIV/STI prevention, including families in interventions for adolescents is age- and developmentally-appropriate. Parents are able to tailor sexual health messaging to meet individual adolescent needs including for example, adjusting information and behavioral skills transfer to align with pubertal transitions, age, gender, and other important life milestones relating to sexual health. Since most adolescents still live with families, parental involvement extends the contact hours and intensity of the intervention by reinforcing motivation and decision-making around protective behaviors within adolescents’ natural ecology. Empowering families with intervention strategies enables them to offer course-correction to support adolescents’ sustained behavior change during a period of rapid life transition. In regards to depression prevention, family

involvement is vital. Adolescents at risk for depression are more likely to come from families with a history of depression given biological and environmental factors that predispose families to depression.[6-9] Parents in South African communities disproportionately affected by HIV are at elevated risk for depression; our preliminary study of N=1,599 parents (M-PI Kuo)[23,24,29] demonstrated elevated risk for depression among families affected by HIV.[25] Moreover, in families where parents are experiencing depressive symptoms, family processes that mediate adolescent risk behavior – such as family communication and functioning – are adversely affected. Our preliminary study of N=4,954 (M-PI Kuo with Cluver) showed adolescent risk for poor psychological outcomes increases if their parents have psychological distress and this is exacerbated by family HIV.[44] Furthermore, parental depression was associated with decreased positive parenting (d=0.27),[80,81] and decreased positive parenting was associated with adolescent depression (d=1.32) and HIV risk behaviors including unprotected and transactional sex (d=0.26).[80,82] Family dynamics linked to adolescent HIV/STI-depression risk reinforce the need to engage families in prevention.

No evidence-based family programs for prevention of adolescent HIV/STI risk existed in South Africa when we developed the *Our Family Our Future* Intervention (M-PI Kuo and Stein's HREC protocols 072/2013 and 796/2014). Two systematic reviews of 31 adolescent HIV prevention and sexual risk reduction interventions in South Africa identified a clear gap, with no empirically tested family interventions for HIV prevention and sexual risk reduction substantively involving parents.[83,84] Since the start of the two previous studies (HREC protocols 072/2013 and 796/2014), two family interventions have emerged. *Let's Talk*, a worksite intervention for parents of 11-15 year olds provides parent-only behavioral training on how to engage adolescents in HIV prevention. The pilot showed beneficial effects on parent-child communication and parent self-efficacy in condom use.[85] Another intervention engaged parents and children (ages 10-14) in HIV prevention, with the pilot showing beneficial effects in parenting involvement and sex communication.[86] For family programs for prevention of adolescent depression, several systematic and narrative reviews detail the efficacy of family interventions [87-89] but no evidence-based family programs for integrated prevention of adolescent HIV/STI risk and depression existed in South Africa when we developed *Our Family Our Future*. Since then, three programs have emerged. The *Vhutshilo* intervention targets adolescents from HIV affected families and provides psychological and behavioral HIV intervention for 14-17 year olds. A cluster randomized controlled trial (RCT) of *Vhutshilo* increased consistent condom use among girls, but not boys; boys were less likely to have risky sexual partnerships but not girls; there was no effect on sexual debut, and there were no biological measures of HIV or STIs.[90] The *Vuka* intervention targets adolescents ages 10-13 years living with HIV and involves caregivers in mental health and HIV prevention. *Vuka* showed feasibility and acceptability.[91] A third intervention still being developed is *South African STYLE*, a family HIV prevention for adolescents in psychiatric care within hospital settings. *Our Family Our Future* will be the first to our knowledge in South Africa to integrate prevention of HIV/STIs with depression in a community setting for adolescents regardless of HIV status or family experience of HIV.

C. METHODOLOGY

1. Investigative Team

Our multidisciplinary team consists of highly qualified, accomplished personnel with expertise in the adolescent HIV, STIs, and mental health in South Africa and globally. We have the ability to recruit, track, and maintain large participant samples to test interventions. We build on extensive experience working with the target population in community settings in South Africa and leverage on successful collaborations and complementary skillsets of our USA-South African investigative team. Dr. Caroline Kuo (M-PI) is a behavioral scientist with over a decade of experience conducting research with adolescents and families infected or affected by HIV/STIs and poor mental health in South Africa. She developed and piloted *Our Family Our Future* in the preliminary studies (HREC protocols 072/2013 and 796/2014), the basis for this efficacy study. She brings expertise in mixed-methods intervention development and testing, and mobile data systems for sensitive adolescent biobehavioral data collection in South Africa. Professor Linda-Gail Bekker (M-PI) is President of the International AIDS Society, Professor of Medicine, Deputy Director of the Desmond Tutu HIV Centre, and Chief Operating Officer of the Desmond Tutu HIV Foundation (DTHF). She is a physician-scientist working on treatment, prevention and care of adolescent populations, antiretroviral roll out, and TB/HIV integration. She will oversee the outcome assessment team, and provide guidance on design considerations for dissemination, scale-up, and implementation. Dr. Dan Stein (M-PI) is Professor and Chair of the Department of Psychiatry and Mental Health at the University of Cape Town. He is a psychiatrist-scientist with extensive experience in mental health intervention development and testing, including work with both adolescents and adults, and in HIV. Dr. Stein will lend clinical expertise for South African mental health, and oversee the intervention facilitator and fidelity team. Dr. Stein mentored Dr. Kuo in the preliminary studies. Dr. Cathy Mathews (co-I) is Chief Specialist Scientist and Director of the Health Systems Research Unit at the South African Medical Research Council, co-Director of the Adolescent Health Research Unit at the University of Cape Town where she is Honorary Associate Professor in the Department of Psychiatry and Mental Health. As an epidemiologist with 20 years of experience in large scale RCT design, she will provide guidance on trial design and biological and behavioral testing for adolescent HIV/STIs. Dr. Mathews mentored Dr. Kuo in the preliminary studies. Dr. Millicent Atujuna (co-I) is a senior social and behavioral scientist at DTHF whose research focuses on adolescents' perceived HIV/STI risk and biobehavioral HIV/STI prevention. She serves as site PI on the CHVI Team in Social and Behavioural Research on HIV Vaccines (THA-118570), End-user Research to Optimize Adherence to Injectable HIV Prevention Approaches (R01 MH105262), and currently oversees the qualitative components of the MTN 020 trial. She will provide social and behavioral expertise, especially on qualitative components and help oversee the team evaluating trial outcomes. She has worked with Dr. Kuo since 2005 and was project coordinator in the preliminary studies. Dr. Larry Brown (co-I) is Professor of Psychiatry and Human Behavior at Brown University's Alpert Medical School, former chair of the HIV Committee of the American Academy of Child and Adolescent Psychiatry, former chair of NIH's CSR Behavioral and Social Sciences Approaches to Preventing HIV/AIDS Study Section, and a member of the Behavioral Leadership Group in the Adolescent AIDS Trials Network. He will lend expertise in integrated HIV-mental health interventions with experience in RCTs of family interventions for mental health and HIV. He was primary mentor on Dr. Kuo's in the preliminary studies. Dr. Tao Liu (co-I) is Associate Professor of Biostatistics, Director of the Data and Statistics Core for the Brown Alcohol Research Center on HIV, and brings ten years of experience as a biostatistician. He will lead statistical analysis, with expertise in statistical methods for longitudinal data, time-to-event data, causal inference, clinical decision making, and with research focused on

HIV in Africa. Dr. William Beardslee (consultant) created the family intervention for depression (*Family Talk*) used as the basis for the intervention in this efficacy study. He is Chair of the Department of Psychiatry at Children's Hospital Boston, Professor of Child Psychiatry at Harvard Medical School, and will guide depression intervention aspects of this efficacy study given expertise in the original intervention. He will not have contact with human participants but will be advising on the training protocol and procedures for the depression component of the intervention.

Hiring and Training Outcome Assessors and Intervention Facilitators. Our research team will initially come from our existing team who worked on the previous study and/or who have previously conduct adolescent focused HIV/STI prevention research and interventions. Then we hire additional team members if needed based on experience relevant to the study. Our team will be split into an outcome assessment team (based at DTHF) for Aim 1 and an intervention team (based at Department of Psychiatry at UCT). We will draw from both for Aim 3. Our investigative team will train our outcome assessment team in data systems, procedures, protocols, and forms using mock training as well as in-field practice to ensure quality data collection and preparation for successful tracking and tracing. Outcome assessors will be *blinded*. We will also train our intervention and fidelity team in protocols, procedures, and forms including randomization and delivery of the *Our Family Our Future* intervention. Training will involve 4 modules. Module 1 includes: 1) introductions and ice-breaking exercises, 2) project overview and training objectives, 3) education regarding depression, HIV, parenting, family communication, gender roles and social norms particularly in regards to sexual relationships, and sexual relationship negotiations. Module 2 focuses on intervention facilitation skills: 1) public speaking and 2) communication of sensitive topics. Module 3 involves training in use of the manualized intervention protocol including: 1) demonstrations of intervention modules, 2) education on core intervention elements, and 3) role-play. Module 4 involves: 1) testing facilitation skills in short mock scenarios, 2) feedback from the PIs. We incorporate challenges that may arise during intervention implementation including delivery of intervention content and inter-personal interactions to assess facilitators' mastery of core. We rank performance using fidelity forms. If an interventionist is not deemed qualified, additional training will be provided until competent. Interventionists deemed unqualified will be replaced.

2. Study design

Summary of scientific design. We test the efficacy of *Our Family Our Future* in a 2-arm, single blinded RCT with 6- and 12-month follow-ups[1]. Participants include a sample of N=880 adolescents 14-16 years (and 880 parents) who will be randomized based on permuted blocked randomization (balancing by gender) to an intervention arm (n=440 adolescents and their parents testing *Our Family Our Future*) or a control arm (n=440 adolescents and their parents) of usual care. Study design carefully adheres to elements outlined in the Consolidated Standards of Reporting Trials (CONSORT) Statement.[92] This pilot study adheres to a single blind, randomized pilot trial design with the end goal of informing a full-powered RCT corresponding to a Phase III

[1] **The 12-month follow-up with parents and teens may occur up to 24 months afterwards in order to retain as many teen/parent dyads as possible in the longitudinal analysis.**

clinical trial. Outcomes will be assessed at baseline, 6 months, and 12 months after the last intervention session. Due to the COVID-19 crisis (March, 2020) we will attempt to first abide by the scheduled 6- and 12-month outcome timepoints for all self-reported and behavioral data with biological data (HIV and STIs) captured when movement restrictions are lifted and/or when physical contact is acceptably safe. If this does not work, we will shift to collecting all 6- and 12-month timepoints for all data to when movement restrictions are lifted and/or physical contact is acceptably safe. The count-down clock for the 6 months and 12 months outcome evaluations will occur after the last intervention session has occurred. Feasibility data and process data on possible mechanisms of change will be collected at eligibility, enrollment, during the intervention sessions, and during baseline and follow-up assessments.

Study questions. The primary study questions are:

Question 1: Is this intervention efficacious? That is, is there evidence of hypothesized effects of the intervention, that the intervention will reduce or maintain symptoms that fall below the clinically significant range for depression and reduce or delay actual or intended sexual risk behavior in adolescents?

Question 2: What mediates and moderates the effect of the intervention on the main outcomes?

Question 3: What are the barriers and facilitators of intervention implementation?

Intervention summary. *Our Family Our Future* is a 'selective' prevention program, designed to address HIV/STI acquisition, sexual risk behavior, and depression among adolescents (ages 14-16) in communities with high HIV prevalence and from families where adolescents exhibit mild, potentially troublesome, depressive symptoms but do not reach the threshold for further screening for a significant clinical depressive disorder. The preventive intervention is comprised of the integration and adaptation of two existing empirically supported models that were ranked "best-evidence" models for preventing HIV (Keepin' It Real) and depression (Family Talk). The two interventions will be integrated into one combined intervention, given the syndemic relationship between outcomes with depression elevating risk for adolescent sexual risk and because the original interventions use similar techniques to improve mood and sexual safety and thus, are appropriate for integration and delivery simultaneously in one adapted intervention.

This intervention involves parent-child dyads who receive the intervention in a community setting, in a facilitated group format. Due to the COVID-19 crisis, we will use an alternative format as an option of individual family sessions with facilitators, delivered by telephone. The intervention is comprised of 3-hour sessions, held weekly for 3 consecutive weeks with an individual family meetings in the third or fourth week depending on family desires. The intervention also includes take-home activities to deepen behavioral engagement with the week's received session and to "prime the pump" for the upcoming week's session. The final intervention covers the following topics in combined adolescent-parent sessions using role play, group activities, discussion and debate, and facilitation: 1) family needs and values; 2) community strengths and challenges; 3) communication skills; 4) talking about sensitive topics – HIV, STIs, sex, puberty, mental health, and discipline; 5) HIV and STI transmission, prevention, and living with HIV; 6) healthy individual and family coping with mental distress, adolescent sexual health, and other challenges; and 7) family goals and strategies for healthy interactions and problem-solving. There are also separate adolescent and parent sessions. For adolescents, topics include: 1) peer influences; 2) healthy relationships and gender roles and interpersonal violence; 3) sexual decision making and communication; 4) condom use and contraception; and 5) consequences of sexual decisions. For parents, these include: 1) adolescent development and reproductive health; 2) healthy

relationships and gender roles; 3) psychoeducation on depression; 4) communicating about sexual and mental health; and 5) condom use and contraception.

We outline signature elements of *Our Family Our Future*:

- **Theory driven and developmentally appropriate adolescent HIV/STI prevention:** *Our Family Our Future's* adolescent HIV/STI prevention components are taken from the original HIV intervention – *Keepin' It Real* – which had some of the largest effect sizes for condom use (d=0.89-1.68) in Johnson's global meta-analyses of 67 adolescent HIV prevention trials.[93-95] *Keepin' It Real* was ranked "best-evidence" by the Centers for Disease Control and Prevention.[96] The theoretical premise of *Our Family Our Future* (and *Keepin' it Real*) is Information-Motivation-Behavioral (IMB) theory and informed by adolescent development theory on the salience of family involvement in prevention.[97-99] The change strategy of the HIV/STI prevention and risk reduction components include: (1) increasing HIV/STI knowledge around protective behaviors (i.e., information), (2) encouraging adolescents to implement protective behaviors through for example, facilitating positive family involvement in addressing adolescent sexual and reproductive health challenges, linking protective HIV/STI behaviors to future goals, and formation of positive peer relationships that impact attitudes towards HIV risk(i.e., motivation), (3) building self-efficacy for prevention behaviors including condom use, condom negotiation, and healthy sexual relationships (i.e., behavior).[97-99] The intervention includes adolescents regardless of HIV status given careful community buy-in that indicated it was unacceptable to further stigmatize children based on HIV positive status by excluding them, and since they are also in need of prevention.
- **Integration of rigorous global evidence on adolescent HIV/STI prevention:** Our adolescent HIV/STI prevention approach was further strengthened with integration of rigorous HIV/STI prevention evidence systematic reviews and/or meta-analyses. The first meta-analysis evaluated effective HIV interventions for South African youth aged 9-26 years (k = 11; N = 22,788) and showed interventions were efficacious in delaying sexual intercourse, increasing condom use, reducing the number of sexual partners relative to those in a control condition, and lowering incidence of HSV-2.[83] Based on this, we will include: delivery by facilitators who are not professionals (e.g., not nurses); delivery over fewer sessions (e.g. length was not important); content covering social norms and gender inequalities; and incorporation of intensive behavioral skills training. We further examined whether brief interventions for HIV prevention have a clinically significant effect in a second meta-analysis evaluating effectiveness of single-session behavioral interventions to prevent STIs (k = 20; N = 52,465); this showed intervention participants relative to controls had significantly lower risks for STIs. Based on this, we focused on a brief but behaviorally intensive intervention since brief preventive (individual, group-based, computer delivered) interventions can have clinical salience.[100] The third meta-analysis evaluated effectiveness of HIV interventions for adolescents 11-19 years globally (k = 67; N = 51,240), and showed intervention participants relative to controls had significant reductions in incident STIs, frequency of sex, number of partners, and significant increases in abstinence or delay of intercourse, condom use, safer sex communication skills, and acquisition of condoms. Based on this, we enhanced the following components: motivational for behavior change and condom skills training but no emphasis on abstinence given abstinence focused interventions were ineffective.[93] The fourth global meta-analysis was on the efficacy of behavioral interventions to increase condom use and reduce STIs (k = 67; N = 40,665) and showed intervention effects of increased condom use, fewer incidents of STIs, and lowered cases of HIV. Based on this, we will include: for motivation, focusing on distal motivation components (i.e., future orientation for adolescents); and content with behavioral skills training (i.e., condom skills and interpersonal skills).[101]
- **Theory driven, best-evidence adolescent depression prevention:** *Our Family Our Future's* adolescent depression prevention components are taken from the original depression

intervention – *Family Talk* – which showed efficacy lowering depressive symptoms (d=0.32), has been adapted for diverse linguistic, cultural, and socioeconomic populations, and was ranked best-evidence by the Substance Abuse and Mental Health Services Administration.[102-109] This intervention is informed by cognitive behavioral theory and resilience theory,[110,111] emphasizing individual- and family strengths, and facilitating resilience-boosting factors such as education, coping, and healthy family interactions. In addition, the intervention is future-oriented to help families develop strategies to cope with forthcoming challenges.[112] The intervention focuses on intervening with families experiencing some distress but not with depression (families with depression need treatment rather than prevention). The change strategy of the depression prevention components include: 1) psychoeducation including specific education of family dynamics of depression; 2) empowering parents to communicate about mental health; 3) cognitive-behavioral strategies including development of recognizing and changing negative thoughts and behaviors and practicing positive coping strategies; 4) supporting healthy family interactions; and 5) creating family strategies and a common narrative around the family experience of mental health.

- **Linkages between HIV/STI and depression:** The intervention increases understanding of linkages between HIV and depression. This includes for example, how negative affect can alter perceptions of risky situations and partners, and how maladaptive coping with emotional dysregulation such as substance use can negatively impact implementation of protective behaviors. This also includes for example how parental depressive symptoms can affect communication and healthy family interactions. The intervention builds self and family efficacy in behavioral strategies to address these interactive risks between HIV/STI risk and depression.
- **Building prevention facilitating family environments:** The intervention incorporates insights from adolescent development theory to build facilitating family environments that can be leveraged to enhance adolescent prevention outcomes.[113] The intervention focuses on family elements critical for both prevention of adolescent depression and HIV/STIs including communication and functioning. The intervention empowers families by using a facilitated process to identify a family's unique strengths and to build on these for maximum intervention impact. The intervention encourages families to map their family's unique goals in their own tailored journey through the intervention and to create family strategies to overcome their specific challenges.
- **Integration of appropriate strategies and modalities for behavior change:** *Our Family Our Future* has been adapted to included visual content to encourage active communication and to overcome low-literacy; and to boost interaction through fun games and debate. The intensity of the intervention is extended through take home activities to reinforce behavior. The intervention is delivered in local language (ixiXhosa) and includes culturally specific concepts of resilience and context specific strategies to build family resilience based on careful formative qualitative work conducted during the K01.[36] The format, delivery, and modality of preventive interventions has been carefully considered to ensure future scalability and sustainability in an overburdened health system with 0.28 psychiatrists, 0.45 other medical doctors, 7.45 nurses, 0.32 psychologists, 0.4 social workers, per 100,000 population in South Africa.[114] Our partnership with Desmond Tutu HIV Foundation (M-PI Dr. Bekker and co-I Dr. Atujuna) – was chosen strategically; they are a large-scale organization capable of bringing *Our Family Our Future* to scale for implementation if found to be efficacious.

Blinding. This will be a single blind study. Intervention participants will not be blinded to the condition they are in (the intervention group will receive the intervention first, with the control group given usual care (*i.e.,* health resources). Study staff (e.g. intervention team) will not be blinded to the condition. Study staff (e.g., assessment team) who assess outcomes after the experimental intervention has been delivered will be blinded to the condition participants have been assigned to. Blinding will be broken for data analysis. To reduce the risk of contamination,

or that blinding will be broken by participants communicating to each other, we will request that participants in the intervention keep all activities and discussions to themselves. We will also assess whether blinding was successful by checking for contamination at the outcome assessments that occurs at 6- and 12-months. There is no chance that dyads in the control group would participate mistakenly in the intervention so we assess for contamination in terms of sharing of intervention materials between the intervention and control group. Dyads assigned to the control group will be screened for contamination. We will adjust for any contamination effects in analyses.

Design considerations – parent involvement and control condition. We carefully considered the choice of one parent participating. For the purposes of this efficacy trial, a consistent parent attending the intervention ensures that we can deliver an appropriate dose of the intervention. For example, consistent participation of one parent enables that parent to better learn the full suite of intervention skills (such as modeling of positive family relationships and communication) needed to support prevention of adolescent HIV/STI and depression. Furthermore, involvement of one consistent parent protects the integrity of the efficacy trial, allowing us to clearly identify what parent should be involved in baseline and follow-up surveys. We additionally clarify that intervention materials have been designed in such a way that they can be used by more than one parent. Given the design of materials where involvement of multiple family members is possible, we are prepared to extend the intervention model to include multiple parents and adolescents in the follow-up of this efficacy trial (if there is evidence of efficacy), which will be an implementation/effectiveness trial.

We chose the control after extensive thought and discussion during trial design. We decided on a control condition of usual care (a packet of existing available brochures on HIV, STIs, mental health including places to access care) based on previous data, ethical and policy considerations, and tradeoffs between cost and science. First, in regards to previous data, the intervention being tested in this efficacy trial (*Our Family Our Future*) is an integration and adaptation of two existing "best-evidence" interventions for HIV/STI and depression prevention. The "best-evidence" ranking for the original HIV and depression preventive interventions used as the basis for *Our Family Our Future* are assigned by CDC and SAMHSA respectively after interventions have shown efficacy in multiple settings and populations. The RCTs of the original interventions were tested using various controls; importantly previous RCTs included time and attention matched controls[94,96] but the original intervention showed superior efficacy. Second, we consider the ethical imperative to investigate efficacy in a manner that is salient and appropriate for the low-resource environment and policy context. There are no existing time and attention matched controls in the research setting we are working in. If we create a time and attention matched control for this trial, policy-makers will not be able to determine whether *Our Family Our Future* is superior to usual care widely available in South Africa; instead, policy makers will only be able to determine whether *Our Family Our Future* is superior to an intervention that does not normally exist in the South African context. Third, we examined what choosing a time and attention matched control would mean for the balance between cost and science. When we examined budget, adding a time and attention matched control – which would need to be newly created in this setting – would result in us shifting significant trial resources. Budget re-allocation adversely affected sample size to a point where power would be compromised. Ultimately, as we look beyond this efficacy trial to an implementation/effectiveness trial, we want to adhere to a design that is most appropriate for the complex ethical, policy, and cost versus science tradeoffs in South Africa. The usual care control condition would allow us to achieve scientific answers with the most

policy relevance, and strike a balance between costs while protecting the integrity of our main scientific goal, to have enough power to thoroughly examine the main outcomes.

Sample Size and Power Considerations. We use data from our preliminary pilot study[35-45] and other relevant secondary sources[78,115-121] to formulate a realistic range of necessary assumptions for sample size and power considerations for primary outcomes. As shown in Table 1 we estimate that a total sample size of 880 adolescents, or 440 adolescents per arm, will be required to adequately power our study.

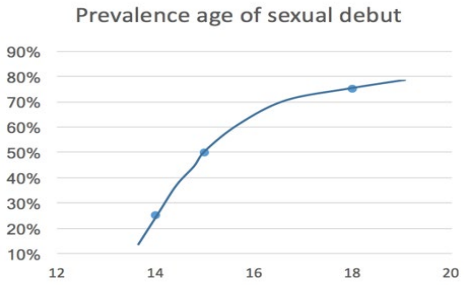
Table 1: Sample Size Estimates

Primary outcome	Control	Intervention	Total sample size	Power (%)
Depressive symptom: Reduced CESD at 12-month visit	25%	50%	880	>95
	30%	50%	880	>95
	35%	50%	880	>95
	25%	40%	880	>95
	30%	40%	880	80
HIV/STI acquisition: prevalent STI at 12-month visit	30%	20%	880	86
	30%	15%	880	>95
	25%	15%	880	91
	20%	10%	880	>95
Sexual debut: Time to sexual debut.	30%*	10%*	880**	>95
	30%*	15%*	880**	92
	30%*	17.5%*	880**	80
	30%*	20%*	880**	60
Risk behaviors: Unprotected sex	17.5%$^{+}$	7.5%$^{+}$	880**	79
	15%$^{+}$	5%$^{+}$	880**	87

*Sexual debut within the 12-mo follow-up among sexually active adolescents at their study enrollment. $^{+}$Risk for sexually active adolescents. ** Shows the total sample size of with an assumption of 50% being sexually inactive at the baseline.

For *depressive symptoms*, we hypothesize that 25%-35% of participants in the control arm will have a reduced depressive symptom scores (on CES-DC) compared with their baseline score; while about 40-50% participants in the intervention arm will have reduced symptom scores. Table 1 shows the study has a power of >0.80 if the difference between the two study arms is Δ=10% or larger. For *HIV/STI acquisition*, we power the study based on the outcome of *any* HIV/STI infection (which we expect to be primarily driven by chlamydia).[119-121] We hypothesize that at the 12-month visit **(which may occur up to 24 months following the 12-month mark)**, prevalence of HIV/STIs will range from 20-30% in the control arm, and prevalence in the intervention arm will be at least 10% lower and ranges from 10-20%. With these effect sizes, the study has a power of at least 0.86 to demonstrate the difference between intervention and control. For *sexual debut*, we assume that about 50% of participants are sexually inactive at study enrollment. Among those who are sexually inactive about 30% in the control arm will have sexual debut during the 12-month follow-up[121] (see Figure 1); and 10-20% in the intervention arm will do so in the same follow-up period. We assume time-to-debut will have an exponential distribution and calculate power using the log-rank test for comparing two survival curves. The study will have a power of >.80 if the intervention can reduce the 12-month debut rate to 17.5% or lower. The study is reasonably powered if the intervention can reduce the prevalence of *unprotected sex (last sex)* by 10% of higher.[78] Loss-to-follow-up is treated as a censoring event. All sample size calculations were carried out using nQuery Advisor 7.0, use a two-side significance level of alpha=0.05, and account for a predicted 15% loss-to-follow-up (the K01 had 100% retention at 3 months for a similar population).[37,39] Our power calculations use outcomes at the last visit or

Figure 1



change from baseline. Including data from all study visits and adjusting for baseline covariates will potentially increase study power to detect difference between the intervention and control.

Language. All study materials and procedures will be conducted in English or isiXhosa. Study materials will be translated by a professional translator, then back-translated to ensure accuracy. Participants will identify language of preference and multi-lingual research assistants (RAs) will conduct procedures in the preferred language. We draw from our established research networks to hire a team experienced intervention delivery, tracking and tracing, and qualitative research with adolescents and families.

Site description. Our trial field site will be at DTHF's Masiphumele community center. This spacious, welcoming facility is ideal for delivery of our interactive family-based intervention, with clinic and lab space to facilitate collection of biosamples for HIV and STIs (for site details, see DTHF's Facilities and Resources). We will move to telephonic delivery of the intervention as an option during the COVID-19 crisis.

Characteristics of the Study Population. We aim for an initial sample size of N=880 adolescent-parent dyads (n=880 adolescents and n=880 parents) for the intervention. Participants will be recruited from the community setting (Masiphumele Community Center and surrounding community. This site has high HIV prevalence and are primarily black African (99%) and isiXhosa speakers (96%).

Inclusion and Exclusion Criteria. We use the following **eligibility criteria** to recruit families into the intervention. Please note that criteria for inclusion of parents was changed from the original grant submission based on critiques of reviewers and requests from NIH. Now parent inclusion criteria reflect more flexibility.

Adolescent *inclusion criteria* are:

1) 14-16 years;
2) concurs that the adult identified is their parent (to also include primary caregivers in the parental role);
3) when more than one child in the family falls within the eligible age range, one child will be chosen at random;
4) lives in the household at least 4 days a week; and
5) sub threshold depressive symptoms (score 6-15) using the CES-DC (child version).

Adolescents will be *excluded* if:

1) they report no or low symptoms (<6) or clinically significant thresholds of depression (16+);
2) If any or both in the adolescent-parent dyad are unwilling to consent and/or assent.

Parent *inclusion criteria* are:

1) 18+ years,
2) parent or equivalent person responsible (as identified by the household);
3) when more than one parent who provides primary care exists in the household, one will be chosen at random to ensure consistency in intervention activities;
4) lives in the household at least 4 days a week; and
5) sub threshold depressive symptoms (score 0-15) using the CES-D Revised (adult version).

Parents will be *excluded* if:

1) they report clinically significant thresholds of depression (16+);
2) If any or both in the adolescent-parent dyad are unwilling to consent and/or assent.

We do not exclude participants based on ethnicity, population, or language groups, but expect that due to the demographics of our study area, we are likely to enroll predominantly isiXhosa, Black African participants. For adolescents, our intervention focuses on preventing HIV risk behavior so adolescents can be sexually active or inactive. We would also like to clarify that our study is not a treatment study and as such, does not enroll psychiatric patients. Instead we focus on individuals that are not meeting clinically significant levels of depressive symptomology based on self-report because this behavioral intervention has a preventive focus. Because we use self-report and non-clinician administered measures to assess possible depressive symptoms, and as such we are not diagnosing mental illness, we will provide a list of clinics where individuals who meet clinically significant levels of depressive symptomology based on self-report so they can be evaluated by mental health professionals. The target population is served by South Africa's public health system, where services are provided for free at point of service.

Inclusion of Minors. This study includes adolescents who are 14-16 years at baseline, and who may be 17 years of age at the end of this study. This population is considered a vulnerable populations. Inclusion of this population is justifiable; conducting research with this population is necessary in order to develop and test evidence-based programs for adolescent HIV risk and depression preventive interventions. This age group was chosen to because these children are entering an age range in which they will be engaging in HIV risk behaviors and elevated risk for depression. As such, they are ideal for a preventive-focused intervention. We recognize that children may be a vulnerable group, and extreme care is required to ensure protection of these participants. Our investigative team has extensive experience in working with adolescents, particularly in regards to mental health and HIV. Because the development and testing of our preventive intervention involves both parents and adolescents, both parents and children provide informed consent and informed assent respectively. All consent and assent forms will be read aloud in participants' chosen language and participants will also be provided copies. Voluntary informed consent (for adults) and voluntary informed assent (for adolescents) participate only after having read/been read aloud the information sheet and had the opportunity to ask questions. To ensure that children do not feel obliged to participate in the research, emphasis will be placed on their ability to refuse to participate, or to cease participation at any point during the research. We emphasize that all information shared with us will remain confidential except for disclosures that fall under legally mandated reporting requirements.

Setting and location. We will recruit from, and conduct this study in a community setting (to maximize external validity/generalizability of trial results). Recruitment will occur within the community center and also in the surrounding community, via house-to-house sampling. The intervention will occur in the Masiphumele Community Center, in a private space in a building that serves the target population.

3. Recruitment and Enrollment

Recruitment setting and procedures. Our trained bi-lingual study team will recruit.

For Aim 1 (efficacy trial), we will recruit N=880 adolescents (and N=880 parents) to test *Our Family Our Future* (described above) in a fully-powered RCT. We will recruit in person through the Masiphumele community site and in the community. We use a recruitment strategy based on "approach all" in both the Masiphumele Community Center (run by the Desmond Tutu HIV Foundation) and surrounding community to limit bias and combat stigma. In the community, we recruit based on procedures used in the preliminary studies. This includes splitting the

Masiphumele community into census enumeration size areas, randomly selecting one area to begin to limit geographical bias. Then, we will systematically recruit by going door-to-door, approaching all for study information and eligibility screening. We visit homes up to 3 times at different times and days to limit day/time bias.

For Aim 2, we do *not* recruit any new participants. This aim is analytical, focusing on the data that was collected in Aim 1.

For Aim 3, For Aim 3 (qualitative component), we recruit a convenience sub-sample of adolescents and parents who were randomized to the intervention arm for in-depth interviews, based on prior participation in the efficacy trial (Aim 1) since planned qualitative interviews in Aim 3, explore the experience of the intervention. The recruitment, consent and assent process for adolescents and parents was described under Aim 1. For stakeholder in-depth interviews, we will recruit individuals that can provide insight into future implementation of the intervention (including intervention facilitators) as well as individuals that may have a stake in future scale-up and implementation of the intervention if shown to be efficacious such as possible future interventionists, program directors, and leadership at DTHF. Stakeholder participants will be recruited through flyers providing contact details for study staff in the community organization work areas. We will also recruit using an initial participant seed pool as recommended by Drs. Bekker and Atujuna. These stakeholders will identify other stakeholders. Staff will speak to interested stakeholders privately by phone or in person. Then study staff will obtain informed voluntary consent.

Eligibility Assessment, Enrollment, and Randomization. The study staff will assess *eligibility*. Eligibility for parents and eligibility for adolescents will be individually determined. Eligibility will be auto-calculated using a pre-programmed computerized method using our secure mobile project-dedicated android phones or “survey devices” that are part of our field-based data collection system (see details on SurveyToGo software used for data collection). The survey devices will automatically calculate eligibility based on the inclusion/exclusion criteria outlined above. Final eligibility will be determined by dyadic eligibility (that is both parents and adolescents have to be eligible to be invited to participate in this family-based intervention). Eligible parent-adolescent dyads will be invited to participate in the baseline assessment and attend an enrollment session where randomization will occur. If interested, each individual in the dyad will be go through individualized informed consent and assent processes. After completing baseline data collection, each individual in the dyad will be issued matching “invitation tickets” to attend the enrollment session. Invitation tickets provide participants with date and location of the enrollment session. These invitation tickets also display unique ID numbers to allow us to verify at the enrollment session that we have screened individuals for eligibility (by matching unique ID numbers on the ticket with our data system) and help us ensure scheduling of dyads. Dyads will attend an enrollment session where trained study staff will answer questions about the study. Following this information session, study staff will gather voluntary informed consent and assent forms from interested individuals. If consent and assent are obtained for a complete dyad, trained study staff will use a computerized block randomization procedure using our FileMaker Software which automatically determines dyad assignment to the intervention or control group based on programming out Dr. Liu and our data team. The block randomization procedure will balance allocation dyads for adolescent gender. Dyads assigned to the intervention group will receive the first intervention session that same day. Dyads assigned to the control group will be given usual care (consisting of a packet of existing available brochures on HIV, STIs, mental health including places to access care). Because randomization occurs in a group setting, assignment is not concealed from participants or from study staff who are part of the intervention team or fidelity

team. However, assignment will be concealed from study staff who are part of the outcomes assessment team (single-blind) so as not to affect assessment of hypothesized effects of the intervention.

4. Research Procedures and Data Collection Methods

All study procedures will be conducted in the language preferred by participants (isiXhosa or English) and all materials will be offered in the language of preference by participants.

Aim 1 - Intervention Procedures. *Our Family Our Future* is a 'selective' behavioral prevention program, designed to address HIV/STI acquisition, sexual risk behavior, and depression among adolescents (ages 14-16) in communities with high HIV prevalence and from families where adolescents exhibit mild, potentially troublesome, depressive symptoms but do not reach the threshold for further screening for a significant clinical depressive disorder (we will recruit adolescents and parents with Center for Epidemiologic Studies Depression Scale scores of 9 to 15, which is a reliable, validated instrument for use in South Africa.) This intervention involves parent-child dyads who receive the intervention in a community setting, in a facilitated group format. Due to the COVID-19 crisis, we will also use, if necessary, a facilitated intervention delivered to individual families by phone. The intervention is comprised of 3-hour sessions, held weekly for 3 consecutive weeks with an individual family meeting in the third or fourth week depending on family desires. The intervention also includes take-home activities to deepen behavioral engagement with the week's received session and to "prime the pump" for the upcoming week's session. The final intervention covers the following topics in combined adolescent-parent sessions using role play, group activities, discussion and debate, and facilitation. In some modules parents and adolescents will have content delivered together and in some modules parents and adolescents will break out to parent-only or adolescent-only groups (the paired facilitators will split apart for these break out groups). The module cover the following for combined adolescent-parent sessions: 1) family needs and values; 2) community strengths and challenges; 3) communication skills; 4) talking about sensitive topics – HIV, STIs, sex, puberty, mental health, and discipline; 5) HIV and STI transmission, prevention, and living with HIV; 6) healthy individual and family coping with mental distress, adolescent sexual health, and other challenges; and 7) family goals and strategies for healthy interactions and problem-solving. There are also separate adolescent and parent sessions. For adolescents, topics include: 1) peer influences; 2) healthy relationships and gender roles and interpersonal violence; 3) sexual decision making and communication; 4) condom use and contraception; and 5) consequences of sexual decisions. For parents, these include: 1) adolescent development and reproductive health; 2) healthy relationships and gender roles; 3) psychoeducation including a focus on depression and child perspectives on depression; 4) communicating about sexual and mental health; and 5) condom use and contraception.

If the intervention is delivered in person, we offer refreshments for families at each intervention session. This intervention will be delivered at the Community Center owned by Desmond Tutu HIV Foundation. The intervention will be facilitated by an interventionist team, and observed by study staff (e.g., fidelity team, supervisor). We believe a trained interventionist team will be appropriate. The original depression preventive intervention (Family Talk) was designed for delivery by a wide range of health professionals. We will use non-specialist but trained intervention facilitators (hired from our pilot study where they were trained) or based on rigorous hiring of those who have previous experience as community health workers, home based care

volunteers, or health educators. We will provide intensive training, fidelity monitoring, and close supervision of non-specialist intervention facilitators to ensure ethical, professional, and quality delivery. We focus on a non-clinical setting because there is limited capacity to facilitate a preventive intervention in clinical care settings with 0.28 psychiatrists, 0.45 other medical doctors, 7.45 nurses, 0.32 psychologists, 0.4 social workers, and 0.28 other mental health workers per 100,000 population in South Africa.[114] We purposefully build community capacity by training non-specialist intervention facilitators. This strategy is consistent with calls for task-shifting as a key strategy for addressing global mental health resource challenges;[122] is cognizant of future scalability and sustainability; and minimizes strain the study might place on overburdened health systems. Task-shifting has been effective in mental health delivery in developing countries[123-125] including depression interventions in South Africa[126] Moreover, non-specialist intervention facilitators from the target community may increase acceptability.[127,128] A study with vulnerable HIV-affected populations showed that non-specialist intervention facilitators were equally as effective as trained professionals, but participants were more satisfied with non-specialist intervention facilitators.[129] Given the setting and context, and the preventive focus of this experimental intervention, this study will task-shift delivery to trained interventionists who have a background that would be contextually appropriate for a community-based intervention for HIV risk and depression and advances family prevention science in South Africa. Trained non-specialist intervention facilitators will deliver the intervention. To support fidelity, trained research staff will be present at all group intervention sessions to offer guidance and supervision to non-specialist intervention facilitators. We will also hold weekly team meetings to discuss the experience of intervention delivery, with the PI and Project Manager offering retraining if needed.

Aim 3 - In-depth interview procedures. Interviews will last 1 to 1.5 hours and take place in a private room at University of Cape Town or in the community intervention site. Due to the COVID-19 crisis, we will default to interviews by phone as needed. Sociodemographic and behavioral data will be gathered during Aim 1. We use a semi-structured agenda to guide qualitative interviews organized by exemplar key questions; exact wording will vary depending on language and cultural norms and will explore these themes: (1) barriers and facilitators to attendance and intervention participation, particularly in relation to scale-up and implementation; (2) acceptability of intervention strategy; (3) predicted behavioral impacts of intervention content including areas that need further refinement and strengthening; (4) advice on format, frequency, timing, and delivery aspects to facilitate future scale-up and dissemination; (5) organizational considerations including advice on gaining buy-in from key gatekeepers; (6) open solicitation of other key considerations for future dissemination, scale-up, and implementation. We record interviews using a digital voice recorder (DVR). At the close of each interview, we will thank participants and provide reimbursement.

Assessment Procedures. Well established measures with good reliability and validity were piloted in the preliminary studies.

Table 2: Outcome Measures and Assessment Timeline

Outcome	Measures	Baseline	3-mth	12-mth
HIV Risk Behavior & Intentions: biologically verified HIV, STIs; prior and planned pregnancy and contraception; sex	• Items taken from South African trials & NIH's Adolescent Medicine Trials Network for HIV/AIDS Interventions; Sexual Experiences Survey[130]	✓	✓	✓

frequency; partner number; condom use; sex refusal				
Depression: depression symptom severity	• Center for Epidemiologic Studies Scale - Revised (CESD-R) adult and child versions[131,132]	✓	✓	✓
Co-variates: socio-demographics; economic status; household characteristics	• Items from the South African Census Questionnaire, World Health Organization Food Security Questionnaire;[133] Verbal Symptom and Autopsy Questionnaire for HIV illness and AIDS orphanhood[31]	✓	✓	✓
Mediators & Moderators: • HIV knowledge; HIV stigma; perceived HIV risk; HIV testing; attitudes and norms around sex, gender, condoms; motivation for abstinence; self-efficacy, and skills • Mental health • Family interactions: positive parenting, monitoring, functioning, bonding, communication • Resilience; social support; substance use	• South African HIV Knowledge;[134] AIDS Related Stigma Scale and Internalized AIDS-Related Stigma Scale;[135,136] Condom Attitudes Scale;[137] Condom Use Self-Efficacy;[138] Condom-use skills checklist[139] • Depression Impairment Scale for Parents,[140] Children Perceptions Of Other's Depression Scale-Mother Version – shortened;[141] Beck Anxiety Inventory and Hopelessness Scale;[142] Children's Manifest Anxiety Scale Revised II;[143] Strengths and Difficulties Questionnaire;[114] National Stressful Events Survey Short Scale and PCL5 for PTSD;[144] K6 for psychological distress[145] • Alabama Parenting Questionnaire-Short Form;[146] Family Relationship Inventory;[147] Family Problem Solving Communication;[148] Parent-Adolescent Sex Communication;[149,150] Inventory of Parent and Peer Attachment;[151] Parental Monitoring Questionnaire;[152] Alcohol Use Disorders Identification Test,[153] Drug Use Disorders Identification Test[154] • Connor-Davidson Resilience Scale;[155] Multi-dimensional Scale of Perceived Social Support[156]	✓	✓	✓
COVID-19 Measures	We use an adapted version of the CRISIS tool from the US National Institute of Mental Health to capture COVID-19 impact (https://github.com/nimh-mbdu/CRISIS)			

We investigate efficacy regarding whether the intervention, relative to the control, will produce: (1) reduced incidence of HIV/STIs; (2) reductions in actual or intended HIV/STI risk behaviors; (3) reductions in depressive symptoms at baseline, 6- and 12-months. For adolescents at each visit, we will capture biologically verified HIV/STIs through HIV tests (dried blood spot) and urine tests for Chlamydia trachomatis and Neisseria gonorrhoeae (Xpert CT/NG assays) (see details on collection, sensitivity, and specificity in Appendices: HIV/STI Test); STIs were chosen based on prevalence in the target population.[119-121] All new positive HIV/STI cases will be referred for treatment at the DTHF youth center clinic or at an appropriate site as per participant. For both adolescents and parents, we also gather self-reported data (noted in Table 2). These data will be captured via our secure mobile data collection device at the household (or by phone if this is not possible after 2 visits; during to the COVID-19 crisis, we will utilize phone collection as the default modality of data collection), guided by trained study staff (e.g., assessment team). We anticipate assessments lasting 1-1.5 hours in home visits, and administered separately to caregiver/parent and adolescent to protect confidentiality. The PIs and/or Project Manager will also monitor assessments, rotating randomly with individual staff in the field (e.g., assessment team) and contactable by cell-phone to troubleshoot with other RAs. Data on initial intervention efficacy will be assessed at 3 time points: baseline, 6- and 12-months post-intervention. The countdown clock for the immediately 6- and 12-month assessments occur starting the first day after the last intervention session and we aim to collect these assessments within a 2-8 week window. During

the COVID-19 crisis, we will make two additional changes. First, regarding the time points, we will try to collect all non-biological data at the 6- and 12-month windows as planned, and then collect the biological HIV and STI outcomes when movement restrictions and/or contact precautions regarding COVID-19 transfer can be reasonably lifted. If this approach results in large amounts of missing data, we will then attempt to collect all data (biological and non-biological data) when movement restrictions and/or contact precautions regarding COVID-19 transfer can be reasonably lifted. Second, during the COVID-19 crisis, we will attempt to collect all data within a 2-8 week window, but will attempt to gather data outside of these countdown windows to limit missing data. In order to increase the reliability of measurements, for data on hypothesized effects, we choose measures informed by preliminary studies, mentor's research in South Africa, and original Family Talk and Keepin' It Real studies to be culturally and contextually appropriate. Measures have been translated previously in South Africa. We also increase reliability by focusing on measures with strong psychometric properties, and when possible with piloting and pre-testing in South Africa. In addition, we increase reliability by programming to decrease human error (e.g., logic scenarios for questions within a skip pattern). Furthermore, for sensitive questions, we administer questions via private earphones plugged into mobile data collection devices using *Audio Computer-Assisted Self-Interview* Software (A-CASI). This method has been shown to diminished social reporting bias. We will not be able to implement A-CASI if we move to remote telephone collection due to the COVID-19 crisis.

We investigate fidelity assessments (coding a minimum of 15% of sessions), we follow recommendations issued by the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium to ensure coding of fidelity based on a standardized monitoring checklist to assess: 1) facilitator adherence/drift from fidelity.[157] These fidelity assessment will be gathered in real time, as intervention facilitators deliver the intervention. We will also gather data to understand attrition which gives us information on another aspect of feasibility. This will include gathering characteristics on who is eligible (from baseline data) but does not attend the enrollment session; data on who fills out baseline, post-, and 3 month assessments; as well as who attends scheduled intervention sessions. We gather process data including data on treatment integrity by examining the rigor of the intervention implementation to the standardized manualized protocol through fidelity data. Fidelity coding will be conducted on 10-15% of total sessions using a neutral coder, ranking integrity and competency of session delivery in real time, and following recommendations issued by the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium[157] We also track recruitment, retention, and attrition data using FileMaker Software to identify ways for optimization of the intervention in future dissemination, implementation, and scale-up should it show efficacy. This will include gathering characteristics on who is eligible (from baseline data) but do not attend the enrollment session as well as who attends scheduled intervention sessions. For *process data* we recruit adolescents, parents, and stakeholders including representatives from DTHF, a well-established community organization that is an ideal target for future scale-up and implementation research for in-depth interviews (N=30-45) with final sample size is based on data saturation. We anticipate these assessments will take 10 minutes. We also gather process data through qualitative in-depth interviews in Aim 3. All measures are provided for full review. There will be no additions to the questionnaire (see Appendix) without approval of the IRB, although some questions may be cut to reduce survey length after piloting.

Retention. We gather information to help track and retain participants including: 1) at baseline, documenting multiple participant contact details (address, phone numbers), names and phones of three individuals who know how to contact the family; 2) monthly contact via telephone or text with reminders for upcoming appointments and to update contact information; 3) geo-

location data to facilitate in-home assessments in a context where homes often do not have addresses or street names. We will also provide participants with reminder cards with study staff contact details and timeframes (and if possible, exact dates), and locations for follow-up data collection We will attempt to contact participants who are not available at home, for participation in follow-up data collection to either meet them at their home or utilize the telephone to complete data collection.

5. Data Safety and Monitoring

Data and Safety Monitoring Plan. Overall internal monitoring of the safety of human subjects will be conducted by PIs. At eligibility screening, those identified with possible clinically significant levels of mental health will be a given list for their nearest mental health service, provided through South Africa's free public health service. This is because this is a prevention study – we offset risk by only including individuals with low levels of depressive symptoms. We screen out those who have progressed to clinically significant ranges. The PIs will oversee monitoring activities. For non-emergency issues, a weekly meeting will be held to address study progress, recruitment and retention, data collection, and other factors related to human subjects and meetings will be held more often if necessary. Emergency protocols will be developed to address serious adverse events and emergency ethical issues should these arise during the intervention or follow-up assessments. Staff will be trained in responses to potential adverse events and given protocol guidelines on how to address these situations. We provide these Standard Operating Protocols or SOPs for review. In cases of adverse events such as identification of depression, suicidal or homicidal ideation, staff will be trained to immediately contact the Project Manager to alert them of the situation. The Project Manager will consult with the PIs to address these issues who are on call at all times during active study recruitment, intervention testing, or assessment. Study staff will be instructed to inform participants they do not have to answer questions that they find too distressing and will be reminded that they can discontinue participation at any time. If needed, participants will be linked to services for stabilization and referral process if they decompensate during eligibility screening, intervention testing, or assessment procedures. Moreover, participants who report significant depression or suicide will not be enrolled in the study (per our exclusion criteria) and will be immediately referred for evaluation and if necessary, psychiatric admission at a local emergency department. Moreover, the Project Manager and PIs should be immediately notified. Participants who develop or report significant depression, suicidal, or homicidal risk during the course of experimental intervention or during assessments will be discontinued and immediately referred for evaluation for psychiatric admission at a local emergency department. All adverse events will be immediately reported to PIs. Serious adverse events will be reported to Brown University IRB/University of Cape Town HREC. A written report will also be given in writing to NIH. All ethical issues will be reported in an annual report to Brown University, University of Cape Town, and NIH.

6. Data Analyses

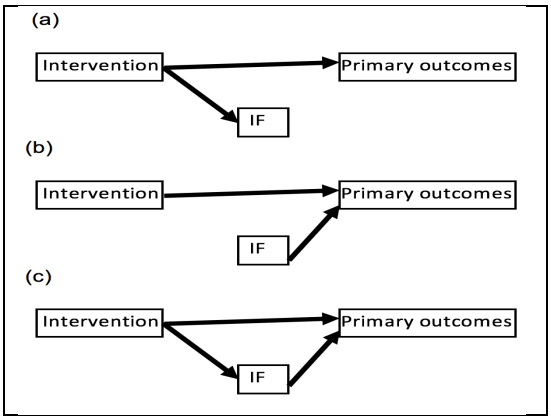
Planned Analyses. We define primary and secondary outcomes, referring back to the study questions.

Question 1: Is this intervention efficacious? That is, is there evidence of hypothesized effects of the intervention, that the intervention will reduce or maintain symptoms that fall below the clinically significant range for depression and reduce or delay actual or intended sexual risk behavior in adolescents?

Analysis plan for Aim 1. We will compare primary outcomes between the two study arms, at 6- and 12-months versus baseline to quantify the intervention's short- and long-term effects. We will compare the continuous and count outcomes (e.g. CES-DC measurement, # of sexual partners, # of sexual episodes without condom) using student's t-test or Wilcoxon rank-sum test (if normality assumption not satisfied), and categorical outcomes (e.g. chlamydia/gonorrhea infection, any STI, frequency of condom use, ever unprotected sex) using Chi-square test or Fisher's exact test (if frequencies are sparse). Changes of outcomes from baseline will be tested using paired t-test, signed rank-rank test, or McNemar's test, whichever is appropriate. For those who are sexually inactive at study enrollment, their sexual debut time will be summarized by Kaplan-Meier curves, and compared using log-rank test. Given that the study has multiple visits, we will use a unified longitudinal model to estimate and draw inference about intervention effects for the primary outcomes. Model (1) is: $h\{E(Y_{ij})\} = \alpha_i + \beta_1 R_i + \beta_2 R_i \times Time_j + \beta_3 X_i$, where Y_{ij} is the outcome at the *j*th visit for the *i*th individual, $h(.)$ is a link function, α_i is a random intercept capturing within-person effect, R_i represents the treatment group membership, $Time_j$ codes the study visit, and X_i denotes baseline covariates. Hence, coefficients β_1 and β_2 represent the difference between the intervention and control and the effect interaction with time; estimation of the two parameters will be our primary interest. Depending on distribution of primary outcomes, we will choose an appropriate link function for Model (1), e.g. an identify link for CES-DC score, log link for # of unprotected sex, and logit link for any STI. As a result, the interpretation of βs will be mean difference, log(risk ratio), or log(odds ratio). We will compare key baseline variables (e.g. age, gender, socio-economic status) between arms to ensure balance of randomization, and make adjustments in the model (by adding the term $\beta_3 X_i$) to estimate treatment effects as needed. Model (1) will be fit using generalized estimating equations to account for repeated measures. For time-to-sexual debut, we will fit a Cox model among those who are sexually inactive at baseline; Model (2) is: $\lambda(t; X_i) = \lambda_{0k}(t) exp(\beta_1 R_i + \beta_3 X_i)$, where $\lambda(t; X_i)$ is the hazard of having sexual debut at time *t* for the *i*th individual and $\lambda_{0k}(t)$ is the baseline hazard. In this model, β_1 is the log(hazard ratio) that captures distributional difference in sexual debut time between study arms. Because time to sexual debut will differ by age, we will fit a stratified Cox model by grouping participants by enrollment age (k = 1, 2, 3 for age=14, 15, and 16) and assuming difference baseline hazard function $\lambda_{0k}(t)$ for each group. Model (2) will be fit using the partial-likelihood.

Question 2: What mediates and moderates the effect of the intervention on the main outcomes?

Figure 2. Causal pathway illustrating the hypothesized relationships between intervention (I), intermediate factors (IF) and outcomes.



Mediation Analysis. We will investigate theoretically-derived mediators proposed to explain the efficacy of Our Family Our Future on prevention of HIV/STI acquisition, reducing HIV/STI risk behavior, and reductions in depressive symptoms. Specifically, we examine whether the extent of impact of *Our Family Our Future* on outcomes is mediated by changes in resilience; behavioral skills and efficacy (e.g., condom use, sex refusal); norms and attitudes relating to sex, condom use, gender; family interactions; and social support. Let us denote these potential mediators as intermediate factors (IF). Our hypothesis is that beside a direct effect on the primary outcome, the intervention can cause changes in these IF at 6-months, which ultimately lead to change in primary outcomes at 12-months. Figure 2 depicts three candidate submodels, using directed acyclic graphs, to represent hypothesized causal pathway leading from intervention to primary outcomes. The full mediation model is given in Figure 2(c), which fully decomposes the effect of the intervention, but contains multiple pathways whose effects are not simultaneously estimable from a single regression model. We will proceed by fitting the following submodels, which we expect will indicate the role of mediators in explaining the effect of our intervention. The time ordering of data collection gives us an excellent opportunity to untangle relationships using causal mediation analysis.[158-162] Submodel (a) describes the causal effects on intervention on the IF and primary outcomes. Given the study intervention is randomized, this submodel is identified by data. Submodel (b) focuses on the causal effects on intervention and IF on the primary outcomes. The effect of IF in Submodel (b) is subject to confounding, and hence its estimation will be based on certain model assumptions (e.g. sequential ignorability). Estimates of submodels (a) and (b) will generate a rough idea of the relative degree to which intervention effect is mediated by each of IF. If the two models suggest a causal relationship between intervention and an IF and between IF and primary outcomes, its mediation effect will be considered in the full model (c) that describes the full process. Thus from analyses of submodels (a) and (b), we will select the best candidate variables with the strongest mediation effects from intervention to IF, and from IF to the outcome. Statistical modeling will utilize causal mediation models,[158] fit using a weighted two-stage regression approach implemented with SAS macros to estimate the full model (c).[163] For our mediation analysis, we will focus on direct and indirection *natural* effects.[164]

Moderation Analysis. We investigate theoretically-derived moderators that may explain responsiveness to *Our Family Our Future* on primary outcomes. Specifically we examine whether the extent of impact of the intervention on outcomes is moderated by the effect of sociodemographics (e.g., gender); severity of parental depressive symptoms, family HIV and orphanhood; structural disparities (e.g., food insecurity); and social protections (e.g., government grants). We will build our moderation analysis around Models (1) and (2) to quantify the moderation effect of these potential factors on the intervention. Specifically, we will add to the two models: their main effects $\beta_3 M_i$ as well as their interactions with the study intervention $\beta_4 M_i R_i$, where M_i denotes the above potential effect moderators at baseline. Our interest is the interaction coefficients β_4, which capture the differential effect of our intervention on the outcome across levels of each of the potential moderators. We recognize possible *limitations*. For mediation analysis, we use a causal inference method based on a potential outcomes framework which

assumes there is no existing unmeasured confounding. Sensitivity analyses will be conducted to examine if assumptions are valid.[165-167] Our causal pathway includes multiple mediators, for which statistical methods are limited but being developed.[163] For moderation analysis, we may not have adequate power to detect all (three ways or higher) interactions between interventions and baseline moderators. However, we expect our approach to provide a foundation for future confirmatory analyses.

Question 3: What are the barriers and facilitators of intervention implementation?

Analyses. For process data on fidelity, we conduct descriptive statistics and summary analysis on the *rigor of the intervention* implementation to the standardized manualized protocol through fidelity data. For in-depth interviews, we conduct ongoing saturation analyses, based on iterative coding during data collection.[168] Each audio recording is transcribed word-for-word and if need be, translated. Transcriptions are checked for accuracy and entered into NVivo. We also enter all observational notes as memos. We analyze interviews using iterative analyses including qualitative research techniques of open and axial coding.[169] Our investigative team will read with a subset of transcripts co-code with discussions to reconcile differences in coding. Iterative analysis helps to develop initial codebook, which is finalized after data collection ends. Codes are grouped into themes and reviewed by the investigative team.

COVID-19 Analyses. We will analyze trial arms to see if there are any differences in main outcomes for the control versus intervention arm during the COVID-19 crisis. We will also examine whether COVID-19 has impacted our main outcomes as compared to other periods of the trial.

D. Possible Risks and Anticipated Benefits and Privacy and Confidentiality

1. Potential Risks and Discomforts to Participants

This research includes a number of potential risks which we outline below. We details procedures to minimize these risks.

1) *Biological specimen collection*. We have carefully considered availability of procedures for age-appropriate biologically verified HIV and STIs. We have sought out the latest available but least invasive methods based on preparatory research of available test kits, assays, lap space, and pricing. As such, we have chosen HIV tests (dried blood spot) which are consistent with what is being done for this age group at clinics and urine tests for STIs (Chlamydia trachomatis and Neisseria gonorrhoeae using Xpert CT/NG assays). We use trained and certified counselors, clinic and lab teams to gather HIV/STI biological data and to conduct referrals for confirmatory testing and treatment.
2) *Sensitive Information*. Participants may feel uncomfortable with the sensitive nature of some of the survey and/or interviews or research staff/counselor's questions. For example, we ask about sexual and reproductive health questions and about mental health. To minimize discomfort, we use a highly trained team (hiring from our pilot study team) who have experience conducting research with families. We also use a computerized mobile smartphone to collect data, which offers privacy both visually and in regards to sound in our deployment of Audio Computer-Assisted Self-Interviewing Software (ACASI) for sensitive questions to limit social desirability bias in participant reporting of data. ACASI procedures will be suspended for phone based data collection during the COVID-19 crisis. The scientific team will train and supervise the RAs in these procedures and techniques to gather data

sensitively. If any such moments of sensitivity occur during the study, the M-PIs will be available for consultation. Further, if participants experience discomfort, they will be given the option of taking a break, or rescheduling. Further, any distress will be minimized by assurances that participants can refuse to provide any data and that they can withdraw from the study at any time without penalty.

3) *STIs and HIV testing*. There is a risk of potential anxiety over being tested for HIV/STIs and special considerations for distress and behavioral changes after testing given our target age group (adolescents 14-16 will engage in biologically verified HIV/STIs). South Africa allows for independent consent of HIV testing to be done at age 12 (our eligibility age is 14-16 years, inclusive). South Africa also allows children to independently consent to medical treatment including pregnancy, HIV testing and use of contraceptives. We follow these ethical and legal norms (which also apply to prevention trials) which include trained pre- and post-test counseling by our trained team (at Desmond Tutu HIV Foundation).[170,171] This pre- and post-test counseling is critical to ensure that: we address pre-test anxiety; we limit any false sense of protection from acquiring HIV and other STI infections that can lead to lead to risk-behavior disinhibition; and that we limit distress upon HIV and/or other STI diagnosis. In addition, we spend significant time during both parent and adolescent consent and assent procedures outlining who, how, and why confidentiality would be breached. We safeguard our participants' confidentiality and privacy. We also explain during the consent and assent under what circumstances mandatory reporting is required. It is also made clear in the consent that health information which is considered private information regarding the adolescent; [172] We explain that adolescents have a right to keep their health information including any HIV and/or STI diagnosis confidential (including from parents), although we will encourage them to disclose HIV and/or STI status and other serious health concerns to a trusted adult in a reasonable time frame (e.g. 3 months) as has been written about by South African researchers and ethicists. We make clear to parents that we will *not* disclose their adolescents HIV and/or STI status or other health information under any circumstance to them or others (aside from the clinic for referral and treatment based on permission of adolescents). We clarify other circumstances in which confidentiality can be breached under pre-specified conditions and to who (such as cases of self or other harm and the legally mandated reporting requirements for disclosure of such information).
4) There is a small risk of *loss of privacy or confidentiality of data*, including sensitive data on sexual behaviors, substance use, and psychological characteristics. We take this risk seriously, and we will take steps to protect participants' confidential data and anonymity. We will ensure that personal identifiers are never included in any research or analytical datasets, or any publications arising from the study. The informed consent documents will bring confidentiality risks to participants' attention and situations under which disclosure can occur (and to who). Names and any other specific personal identifiers will not be included in any datasets: only a unique participant RIN. Tracking information (including names and telephone numbers) will be available solely to the project staff in charge of planning and organizing follow-up visits. We explain the extensive data protections put into place for our data above (see Data Collection, Management, and Protections). The informed consent and assent documents will highlight confidentiality risks.
5) This is *not a treatment study* and as such, does not enroll psychiatric patients. Instead we focus on individuals that are not meeting clinically significant levels of depressive symptomology based on self-report because this behavioral intervention has a preventive focus. *Our study is focused on depression prevention.* We conduct a 'selective' preventive intervention where we are selecting for adolescents at elevated risk for depression onset. We use self-report and non-clinician administered measures to assess possible depressive symptoms (using the Center for Epidemiologic Studies Depression Scale – Revised (version for adults and children, a validated and reliable depressive symptom measure in South Africa),

and as such we are not diagnosing mental illness. However we acknowledge that participants may experience *psychological decompensation*. If this occurs, they will be withdrawn from our prevention focused trial. For these participants, we will provide a list of clinics where individuals who meet clinically significant levels of depressive symptomology based on self-report so they can be evaluated by mental health professionals. The target population is served by South Africa's public health system, where services are provided for free at point of service.

6) Participants may experience *stigma or discrimination* due to HIV and/or STI status and mental health. We take this risk very seriously. We have taken steps to minimize the risk that participants' HIV/STI status may be revealed due to association with our pilot study (through careful discussion of testing decisions for adolescents in our trial, and careful discussion of confidentiality with both parents and adolescents as explained above). We also put in place data handling, storage, and analysis practices to protect participants' anonymity. We will provide training for all project staff on the needs and strategies for maximizing participants' anonymity. Our Community Advisory Boards will also advise us on how to minimize social harms to participants due to stigma and discrimination.
7) *No increases in risk*: No subject will be "enticed" to engage in additional risk to become a participant. We implement consent and assent procedures that build in time for consideration of benefits and harms, and in a proactive engaging discussion of consent and assent considerations that explicitly avoids a "pro-trial enrollment" position.

2. Protection against Possible Risks

Protection against risk. Trained and qualified research assistants will collect data. All participants will be advised of their right to skip any questions or refuse participation in any parts of the study. All efforts will be made to protect the well-being of the participants. We will provide an information sheet to every participant including resources for: (a) the Child Protection Unit (a specialized branch in the South African Police Services), (b) voluntary counseling and testing services for HIV infection, (c) telephone hotlines, (d) psychiatric services. We also make clear on the consent form language that advises youth and parents that disclosure of incidents that require mandatory reporting to South African officials (e.g., threat of harm to self or others, child abuse) will be reported to the appropriate officials. We make clear what situations would require permission to break confidentiality (such as referrals to clinics).

Community Engagement. Our community engagement process will help us protect again risks. First, we will consult with Desmond Tutu HIV Foundation's two long standing community advisory boards. One community advisory board is comprised of 15-20 adults from community organizations and non-governmental organizations, community leaders, and others. The other community advisory board is comprised of 15-20 youth including teenagers and young adults years who are leaders from youth groups in schools, organizations working with young people, and both living with HIV and affected by HIV. These boards provide scientific feedback on all aspects of study including protocols, materials, recruitment, retention, and dissemination strategies. The boards also provide advice to troubleshoot any unanticipated challenges throughout the active study phases and in the dissemination phase. Second, our community engagement activities – led by Mr. Ntando Yola, who has worked in community engagement for 12 years, and has extensive experience in the specific population, topics, and community setting that our study is targeting – will include a wide range of consultation and engagement meetings. These typically consist of open community consultations and one-one-one meetings with key organizations and gatekeepers. The activities of this office are critical for DTHF's success in trial retention in other community-based trials. Third, based on community advisory board and

community engagement processes, we will develop a tailored dissemination plan (which will be continually refined in the study lifecycle) that includes optimal target venues, campaign strategies, and information/education needed to keep the community engaged. We anticipate for this study, our engagement campaign will include the following venues: schools, youth centers, community meeting locations, and public spaces such as those where social grants and community celebrations are held.

Planned Procedures for Protecting Against or Minimizing Potential Risks. For adolescents, during assent procedures, and for parents during consent procedures, we highlight the legal norms that would require break in confidentiality, and who information would be reported to. First, we detail the type of health information that cannot be disclosed with adolescents' prior permission; [172] for example, we will seek adolescent permission to disclose their information to the clinic for confirmatory HIV/STI testing and treatment, and to elicit confirmation of their treatment for curable STIs from the clinic. We explain that adolescents have a right to keep their health information including any HIV and/or STI diagnosis confidential (including from parents), although we will encourage them to disclose HIV and/or STI status and other serious health concerns to a trusted adult in a reasonable time frame as has been written about by South African researchers and ethicists. Second, we make clear to parents that we will *not* disclose their adolescents HIV and/or STI status or other health information under any circumstance to them or others (aside from the clinic for referral and treatment based on permission of adolescents). Finally, we clarify other circumstances in which confidentiality can be breached under pre-specified conditions and to who (such as cases of self or other harm and the legally mandated reporting requirements for disclosure of such information).

For our data, we will minimize loss of privacy by limiting access to individually identifiable information using unique RINs on all paper, electronic data, and analyses. Data, including digital voice recordings and data collected via ACASI will have several protections. First, all data will be stored on password-protected computers including project dedicated smartphones and files. Second, all files on project computers and smartphones will be further protected by nCrypted Cloud software which offers two-way encryption with secure access controlled by PIs (who can turn on and off access to password protected files from a central location) and wipe all data from devices remotely in the case of theft. NCrypted Cloud also enables the PIs to control who has access, who can move files from the secured and encrypted cloud serve onto local hard drives (including computers, smartphones, and external harddrives), and whether and how files can be moved between providing absolute control over data management and monitoring. Third, all staff will be trained in procedures for maintaining confidentiality of participant information. We are also prepared to address any distress that may arise by referring to South African's mental health care within their free public health systems. All serious adverse events will be reported to IRB and NIH. Overall internal monitoring of the safety of human subjects will be conducted by the M-PIs. For non-emergency issues, a weekly meeting will be held to address study progress, recruitment and retention, data collection, and other factors related to human subjects and meetings will be held more often if necessary.

During the COVID-19 crisis, we have taken additional steps to minimize risk to participants and our team of COVID-19 transmission. We have shifted all non-biological data collection to phone remote collection to limit physical contact between the team and participants for non-biological data. Biological data (HIV and STI data) is collected at the clinic operated by the Desmond Tutu HIV Foundation. This clinic remains open for all services with new protections

measures in place including the use of PPE, social distancing, and new scheduling procedures to limit waiting in line and crowds at the clinic, etc.

Additional Protections for Children. We put into place additional protections for children since adolescents who are 14-16 years of age will be in this study. We recognize that children may be a vulnerable group, and extreme care is required to ensure protection and empowerment amongst participants but that exclusion of this group would significantly prohibit scientific development in topic areas of great importance to the health and wellbeing of this group. To ensure informed consent and assent, we will clarify what information will be kept confidential and what will be disclosed to another party. We also build upon our team's extensive research and clinical experience working with adolescents affected by HIV, STIs, and poor mental health in South Africa as well as our team's experience conducting biobehavioral research with vulnerable populations affected by HIV in South Africa and other international settings. We provide additional protections in consent and assent procedures. All informed assent forms will be read aloud in participants' chosen language and participants will also be provided copies. To ensure that children do not feel obliged to participate in the research, emphasis will be placed on their ability to refuse to participate, or to cease participation at any point during the research. As has been the practice in our previous studies with this vulnerable population, our research team is trained to recognize that any avoidance by children of the research will be taken as evidence of failure to assent. For adolescents, during the parental informed consent procedures and during the adolescent informed assent procedures, we emphasize that all information shared with us will remain confidential except for certain information requiring their permission to disclose (HIV, STI, and other mental health); we will also detail mandated disclosures in the case of harm to self or others, age-differential partners, exploitative sex, perpetration with identifiable rape victims, being a victim of rape, sexual abuse or physical abuse which falls under legally mandated reporting to police, social services, and IRB.

Data Protected by Unique Research ID Number (RIN). Every individual that expresses interest in our study and is deemed eligible will be assigned a RIN. All data they provide will be identifiable only by the RIN, which will not contain any personal identifiers. During this study, we will take precautions to separate any documents that identify participants by name from documents that contain participant data. Documents that identify participants by name will include the password-protected file containing participants' signed informed consent/assent forms and signed documentation that participants have received reimbursement. These documents will be kept entirely separate from any documents containing participant data. Paper documents that identify participants by name will be kept in locked cabinets in the offices of study personnel. Data will also be backed up regularly, and to facilitate quality checking and monitoring.

Training in Confidentiality. The M-PIs will provide the study team with training in all ethical procedures including informed consent/assent, maintaining confidentiality, and protecting confidential data. This training includes for example, the importance of securing participants' privacy, the separation of data from identifiers, and protocols for using locked offices, filing cabinets, and password-protected files to avoid unauthorized use of participant data. The study team will meet regularly to discuss protocols for maintaining participants' privacy. The study team will also follow institutional policies for requiring mandatory training in human subjects protection before conducting any study activities.

Data and Safety Monitoring Plan. To comply with the NIH policy for Data and Safety Monitoring, we will create a system for oversight of the project. Oversight of internal monitoring of

the participants' safety will be conducted by the project's MPIs and Co-Investigators. Investigators will communicate bi-weekly on the project (either in person or by conference call), at which time they will evaluate study progress, review data quality, recruitment, and study retention, and examine other factors that may affect outcomes. They will review any adverse events to determine any changes in participant risk. Investigators will be available to meet outside of these regular team meetings as needed, including discussion of concerns regarding a particular participant or any problems that may arise for participants. If necessary, they will make appropriate recommendations for changes in protocol. Any adverse events that are observed and/or reported will be immediately reported to MPIs. Serious adverse events (SAEs) will be reported to the Brown University and UCT IRBs/HREC immediately. Adverse events will also be reported *annually* to the Brown University and UCT IRBs/HREC as well as to the appropriate NIH institute.

At eligibility screening, those identified with newly diagnosed HIV and STIs will be offered referral to care and treatment. This process will be repeated at 6- and 12-month follow-up time points. At eligibility screening, participants who report significant depression or suicide will not be enrolled in the study (per our exclusion criteria) and will be immediately referred for evaluation and if necessary, psychiatric admission at a local emergency department. Suicidal admission will result in immediate notification to the Project Manager and PIs. Participants who develop or report significant depression or suicidality during the course of experimental intervention or during assessments will be discontinued and immediately referred for evaluation. Those with clinically significant levels of depression will be a given list for their nearest mental health service (as defined by our reliable, valid symptom measure for depression) provided through South Africa's free public health service. This process will be repeated at 6- and 12-month follow-up time points. This is because this is a prevention study – we offset risk by only including individuals with depressive symptoms below the clinically significant range for depression. We screen out those who have progressed to clinically significant ranges for depression. Standard Operating Protocols have been developed to address serious adverse events and emergency ethical issues should these arise during the intervention or follow-up assessments (see Appendices). Staff will be trained in responses to potential adverse events and given protocol guidelines on how to address these situations. In cases of adverse events such as identification of depression, suicidal or homicidal ideation, staff will be trained to immediately contact the Project Manager to alert them of the situation. The Project Manager will consult with the PIs to address these issues who are on call at all times during active study recruitment, intervention testing, or assessment. Study staff will be instructed to inform participants they do not have to answer questions that they find too distressing and will be reminded that they can discontinue participation at any time. If needed, participants will be linked to services for stabilization and referral process if they decompensate during eligibility screening, intervention testing, or assessment procedures.

2. Benefits to Participants

The goal of this study is to promote healthy sexual behaviors and mental wellbeing among adolescents. Families will be involved in an intervention which aims at increasing knowledge, changing attitudes and beliefs, increase self-efficacy, increasing family bonding and communication, and developing individual family strategies to improve adolescent sexual and mental health. There may be little or no direct benefit to participants from the study. Some possible benefits may include the following: (1) Management of HIV/STIs. Adolescent participants will receive diagnostic evaluation for HIV/STIs and with their permission, referral to confirmatory

testing, care and treatment for the HIV/STIs being evaluated in our protocol. (2) Participants will receive information on HIV, STI, and mental health along with general health, and social services and referrals if necessary. (3) We believe the risks associated with this prevention research are reasonable in relation to the anticipated benefits of advancing empirical knowledge on prevention approaches for this high priority population and setting.

3. Benefits to Science

There are no existing evidence-based alternative treatments based on rigorously tested integrated HIV/STI-depression preventive interventions exist for adolescents taking a family approach in South Africa. This is not a treatment study but has a prevention focus. For any unexpected adverse event, we will follow reporting requirements as mandated by legal requirements in South Africa and link to appropriate support via South Africa's free public health service system. In our weekly team meetings, we explicitly probe for any unanticipated ethical situations which do not need immediate emergency attention. All ethical emergencies requiring urgent attention are reported to the M-PIs immediately. All procedures will be reviewed by IRBs. Participants will receive a list of resources of resources for health and social services. For mental health, we specifically promote access to information about Childline (for adults Lifeline), Stop GBV helpline, HIV helpline, FAMSA and the South African Depression and Anxiety Group (SADAG) helpline. In our weekly team meetings, we explicitly probe for any unanticipated ethical situations which do not need immediate emergency attention. All ethical emergencies requiring urgent attention are reported to the PIs. All procedures will be reviewed by institutional IRBs.

To our knowledge, *Our Family Our Future* will be the first South Africa family-based intervention to integrate prevention of HIV/STIs with depression in a community setting for adolescents regardless of HIV status or family experience of HIV. Testing the efficacy of a family-based, resilience-oriented intervention model that prevents HIV risk and depression may be beneficial. We also build from two existing evidence-based interventions (*Family Talk* and *Keepin' It Real*). Given strong evidence behind these models and the preventive focus on the this behavioral intervention, we believe the risks of the proposed study are reasonable and balanced by the potential contribution of developing an efficacious family intervention to reduce public health burdens in HIV-endemic communities. Currently two family interventions existing which focus on HIV prevention for similar age groups in South Africa. *Let's Talk*, a worksite intervention for parents of 11-15 year olds provides parent-only behavioral training on how to engage adolescents in HIV prevention. The pilot showed beneficial effects on parent-child communication and parent self-efficacy in condom use.[85] Another intervention engaged parents and children (ages 10-14) in HIV prevention, with the pilot showing beneficial effects in parenting involvement and sex communication.[86] Our pilot of *Our Family Our Future* showed a broader range of promising directional effects for HIV/STI prevention. For family programs for prevention of adolescent depression, several systematic and narrative reviews detail the efficacy of family interventions [87-89] but no evidence-based family programs for integrated prevention of adolescent HIV/STI risk and depression existed in South Africa when we developed Our Family Our Future. Since then, three programs have emerged. The *Vhutshilo* intervention targets adolescents from HIV affected families and provides psychological and behavioral HIV intervention for 14-17 year olds. A cluster randomized controlled trial (RCT) of *Vhutshilo* increased consistent condom use among girls, but not boys; boys were less likely to have risky sexual partnerships but not girls; there was no effect on sexual debut, and there were no biological measures of HIV or STIs.[90] The

Vuka intervention targets adolescents ages 10-13 years living with HIV and involves caregivers in mental health and HIV prevention. *Vuka* showed feasibility and acceptability.[91] A third intervention still being developed is *South African STYLE*, a family HIV prevention for adolescents in psychiatric care within hospital settings.

E. Securing Participants' Informed Consent and Assent

Study Terminology Relevant to Consent and Assent Procedures. In this study, we used the term parents to describe adults serving in a parental role and may include biological parents as well as surrogate parents. Diverse child caring arrangements are common in the South African context, where a large number of non-biological caregivers take on the parental role. The South African Child Gauge 2013 Report by the Children's Institute shows that approximately a quarter of all children in South Africa do not live with either biological parent. More importantly, among the populations which we are working with (largely black African), approximately two-thirds of children do not live with either biological parent. Biological parents may not present in children's lives due to cultural norms, personal family choice, labor migration, parental neglect, social circumstances, etc. These diverse family structures result from historical adaptations due to separation of families during apartheid, economic migration, etc.[173,174] Furthermore in our study setting, many children have experienced the death of biological parents due to HIV/AIDS or other causes. In HIV-affected communities, informal caregiving arrangements, in which non-biological individuals playing a parental role are particularly prevalent.[175,176] We have utilized consent from caregivers in our previous studies which have been reviewed and approved by South African universities (University of KwaZulu Natal, University of Cape Town and provincial Departments of Health and Education) and also by Oxford University.

The overriding principle in all scenarios related to the informed consent and assent process will be that any decision will be in the best interests of the adolescent. Our consent procedure complies with section 3.2.2.3 of the Department of Health guidelines for orphans without guardians (Ethics in Health Research. Principles, Processes and Structures from the Department of Health 2015). We will seek consent from parent substitutes as described in section 3.2.2.3 and as described in our protocol. We believe our research meets all three conditions set out in the guidance. The risk standards as set out in 3.2.2.1 b are adhered to. In the protocol, we identified the risks as low to medium and we described 5 steps we would take to minimize the risks. We believe the research involves greater than minimal risk of harm but provides the prospect of direct benefit for the minor, in the form of the knowing their HIV and STI status and receiving appropriate referral to health and social services. The research also has a high probability of providing significant generalizable knowledge in the form of knowledge about the effects of a multi-component HIV and depression preventive intervention for a population at high risk of HIV. In addition, it is not possible to do the research with adults: we have described why it is not possible to do the research with adults in the justification which we included in the protocol, and which is appended here. The research proposes to investigate a problem of relevance to minors: We have described in the protocol why this research on HIV and depression prevention is of relevance to minors. We detailed what adults can qualify as parental substitutes clearly in the consent forms and here as well: If no parent, then guardian: (1) either court-appointed OR as indicated by the parent in a Will (s 27 Children's Act) iv. If no guardian, then foster parent (per order of Children's Court) (Note that social workers should request that the authority to give permission should be included expressly in the court order authorizing foster care); (2) If no foster parent, then caregiver (s 1 Children's Act: defined as '…any person other than a parent or

guardian, who factually cares for a child and includes – a) a foster parent; b) a person who cares for the child with the implied or express consent of a parent or guardian of the child; c) a person who cares for the child whilst the child is in temporary safe care; d) the person at the head of a child and youth care center where a child has been placed; e) the person at the head of a shelter; f) a child and youth care worker who cares for a child who is without appropriate family care in the community; and g) the child at the head of a childheaded household'); (3) If minor is caregiver in child-headed household and no supervisory adult (s 137 Children's Act), then trusted adult nominated by minor, including but not limited to social worker, community worker or teacher; (4) Minors' independent consent in particular circumstances for reasons of sensitivity. Our approach is consistent with guidance from University of Cape Town's HREC SOP on research with children (http://www.health.uct.ac.za/fhs/research/humanethics/sop).

Consent and Assent Procedures. For eligible participants, we will proceed with written informed consent and assent. For all consent and assent procedures, trained study staff will read aloud the consent and assent forms and also provide written copies for eligible and interested individuals to follow along with. Each person will be given time to consider the information and to ask questions. Signed informed consent and assent forms will be kept by study staff and a copy of the consent and assent form will be provided to participants for their records. We also electronically image capture the consent/assent signatures within our secure data system – SurveyToGo – used in our previous HREC approved protocols. For Aim 1 (the efficacy trial), consent and assent procedures will occur at two time points. First, consent and assent will occur at the first point of contact, after screening for eligibility and prior to gathering baseline assessment. We will be obtaining "active" adult consent, where written consent is needed prior to becoming involved in research. If parental and caregiver consent is given, we will obtain "active" child assent. Adolescents will also be told that even if their parent has already signed parental consent, that they may still change their mind and decide to not participate without any penalty. To ensure that children do not feel obliged to participate in the research, emphasis will be placed on their ability to refuse to participate, or to cease participation at any point during the research. We emphasize that all information shared with us will remain confidential except for conditions needing permission from participants for referral to confirmatory testing and/or treatment and disclosures that fall under legally mandated reporting requirements. Because the development and testing of our preventive intervention involves both parents and adolescents, both parents and children provide informed consent and informed assent respectively for participation. In our study, we use the term parent broadly to describe adults serving in a parental role and may include biological parents as well as surrogate parents.

We will be obtaining "active" adult consent, where written or electronically generated signature consent is needed prior to becoming involved in research. Moreover, we will obtain "active" parental or caregiver consent before a minor can become involved in research. If parental and caregiver consent is given, we will obtain "active" child assent. For all participants, the study team will describe the research study, answer any questions or address any concerns, and assure that individuals fully understand what their own and/or their child's participation in the proposed study entails. During the informed consent procedures, all possible risks that may be experienced as a result of participating in the research study will be brought to the potential participant's attention. Once the study team member is assured that potential participants have a clear understanding of the information in the consent form, they will be asked to sign the consent forms. Once parents and caregivers have given consent, informed assent will be sought from the adolescents. During the informed assent procedures, adolescents will also receive a description of the study, including what their participation entails and the possible risks they may experience

as a result of participating in the proposed study. Adolescents will also be told that even if their parent has already signed parental consent, that they may still change their mind and decide to not participate without any penalty.

In Aim 1, Consent and assent procedures will occur at two time points – for baseline and for randomization with the remainder of trial participation. If parents are not present at the Community Center, then study staff will gather parent contact details to proceed with the *parental consent* process. If at the Community Center, interested adolescents will be sent home with written parental consent and adolescent assent forms. Study staff will speak with parents by phone or in person to secure consent. During this conversation, the parent will receive information on the study. Parents will have time to consider the information. Then they will be asked if they give consent for the adolescent to proceed with assent. Study staff will request a written informed consent form from parents and prompt them to keep the second copy for their records. For consenting adolescent-parent dyads, a participant locator form will be filled out to help schedule baseline assessment and for the enrollment session where randomization will occur prior to the first intervention session. Consent and assent will occur at the first point of contact, after screening for eligibility and prior to gathering baseline assessment. We purposively separate consent and assent procedures into two phases to provide adolescents and parents additional time to consider consent and assent – following best ethical principles for multiple of "continuous" consent[177] – in working with potentially vulnerable populations. Consent and assent will be sought again after the enrollment session which serves as a behavioral run-in that involves an intensive discussion of pros and cons of trial participation. We implement a method used by Dr. Michaela Kiernan (a faculty member at the NIH Randomized Behavioral Clinical Trials Institute which Dr. Kuo attended)[178] in her behavioral trial work. This method focuses on thoroughly discussing ethical considerations prior to randomization (and in doing, also optimizing recruitment and retention in the trial). This procedure involves a discussion of pros and cons in the order shown in Figure 2 as part of study orientation, prior to randomization.

Figure 2: Study orientation and ethical discussion		
	Enrolling in the study	**NOT enrolling in the study**
Pros of participation	3 – Discuss third *pros* of enrolling in the study	2 – Discuss second *pros* of *not* enrolling in the study
Cons of participation	4 – Discuss last *cons* of enrolling in the study	1 – Discuss first *cons* of *not* enrolling in the study

The idea of this behavioral run-in is to provide a more in-depth orientation session after participants have been given time to consider the study in depth (following an initial consent and assent at baseline). In this behavioral run-in, we provide a thorough discussion of ethical considerations to complement traditional consent/assent procedures. This discussion focuses upon eliciting potential participants' perspectives of pros and cons of their potential trial enrollment to help them consider risks and benefits thoroughly, to explicitly acknowledges study challenges, and to engage in a meaningful interactive dialogue to overcome any misunderstandings of the study (including confusion on trial design and objectives, prevention misconception, and other ethical challenges documented by studies on related topics in similar settings).[179,180] The approach avoids a "hard sell" or "pro-change" positions, but instead, focuses on enriching the informed consent and assent process to ensure meaningful informed and voluntary consent and

assent. This second stage consent and assent process includes an option for choosing to participate in Aim 3 for adolescents and participants. For Aim 3 stakeholder in-depth interview participants, we will secure written voluntary informed consent before proceeding with interviews.

Consent Form Labeling. We learned a great deal in preliminary studies about designing a family friendly program including naming of materials. This issues of HIV-fatigue and stigma of both HIV and depression were highlighted suggesting that the program name should not include these terms. Aim 1 participants describes a family friendly program and generated possible program names which emphasized family empowerment, unity, and learning in the program name. As such, we have chosen to prominently reflect a positive program name in the study materials (recruitment, outreach, consent and assent forms, etc.) and not to use the scientific study name to increase acceptability with the target study population and in the study community. We come up with the program name of, "Our Family Our Future" based on concepts and words identified preliminary studies.

Storage of Informed Consent and Assent Forms and Participant Contact Details. Signed informed consent and assent forms will be stored securely in a locked cabinet in project offices for the duration of the study and analysis. Following the completion of study analyses, they will be stored for 5 years. Participant contact details will be stored in a password-protected electronic file on the project drive, separate from any participant data. We will keep participant contact details until the conclusion of the study, and then we will destroy them. If participants give written permission for us to keep their contact details for future Aims of this study and future studies, we will maintain their information for that purpose in a password-protected log entirely separate from this study's records.

F. Privacy and Confidentiality

Data Privacy and Protections. Every individual that expresses interest in our study and is deemed eligible will be assigned a Unique Research ID Number (RIN). All data they provide will be identifiable only by the RIN, which will not contain any personal identifiers. Data is identifiable information is aggregated into a separate electronic file than other data (using our pre-programmed data collection system. Paper documents that identify participants by name such as consent and assent forms will be kept in locked cabinets in the offices of study personnel. Only lead investigators or essential project staff will have access to project data. A database that will serve as the identifier key will contain the participant's RIN and contact details. This database is the only record that could be used to link participant data to his/her identity. This database will be stored on a secure project drive and protected by an electronic password, and it will be accessible only to study personnel. All analyses will be conducted solely according to RIN, and any individual participant identifiers will be expunged from data used for analysis.

We use several data systems to protect our data. All data systems have stringent protections for human subjects data and have been piloted and tested in our preliminary studies in South Africa. First is **Filemaker**, our randomization program and tracking database. This is stored on Brown University's encrypted server and this database is only available to staff tracking participants. It is password protected (in addition to accessibly only by a password protected computer. We also utilized **SurveyToGo Software (http://www.dooblo.net/stgi/surveytogo.aspx).** SurveyToGo will be used to screen for eligibility, and to collect data at baseline, immediately post-intervention, and 3 month assessment. Data center security is protected by state-of-the-art servers hosted by Amazon AWS. Amazon AWS datacenters are housed at nondescript facilities protected by biometric locks and round-the-clock interior and exterior surveillance monitoring. Data center is limited to authorized personnel, who

must pass a two-factor authentication a minimum of two times to access the datacenter floors. The software and infrastructure are updated regularly with anti-virus protection and regular security updates. Network security includes an enterprise-level firewall that protects two way data flows. This includes SSL encryption to protect device to server communications and management applications to server communications. SSL certificates are also utilized and al data passes through a checkpoint firewall product to prevent network attacks. All network traffic is stopped at the firewall and monitored with Intrusion Detection and Prevention Systems. Data is strictly regulated. This includes security measures to ensure that data is tied to, owned by, and accessible only by our project team for each specific project. Access to SurveyToGo system for our project team and project is done via user name and password which authenticates authorized access. In addition, we can grant various levels of security and access with delineated rights to data in the project. This role based security can provide a combination of access features including combinations of the following: creating users for the SurveyToGo project, managing storage of data, managing rights to access, viewing rights. This includes the ability for our project team to delete and wipe all data from SurveyToGo servers. Data collection security includes the ability to collect data from the field (in our case using android devices that are password protected and with ncrypted cloud security). SurveyToGo data systems on Android devices will route encrypted data to a secured local database; this data is automatically uploaded to the SurveyToGo remote server and deleted from the device whenever network is detected. If network fails, data can still be collected in offline scenarios and is fully encrypted in this scenario. SurveyToGo allows us to disable devices that may be lost or stolen by de-linking devices to the specific SurveyToGo project immediately or using the auto-sync option of 10 minutes to pull any remaining data from the device. Data stored on a PC includes a built-in encryption mechanism of the Microsoft SQL Mobile to encrypted data on the local hard drive of the machine. We use a scanned teleform system for paper data collection. All paper versions are stored in locked study cabinets in project offices upon scanning. The scanned versions are stored on **Ncrypted Cloud** which offers similar state of the art protection as detailed for SurveyToGo. Ncrypted Cloud includes double encryption, zipping of files, password protected entry to folders and files each and every time or once, authorization of every user by the PI. This program also allows the PI to track which authorized individual has accessed files and when and changes that have occurred including deletions, copies. The PI can bar all copying or set limits to copying of files. Importantly, data is wipeable via “unlink” function from a central location in case of theft or loss. To guard against accidental data loss, the project data will also be backed up onto a password-protected external storage device (e.g., an external hard drive, which will be kept in a locked project office).

Training in Confidentiality. The PIs will provide the study team with training in all ethical procedures including informed consent/assent, maintaining confidentiality, and protecting confidential data. This training includes for example, the importance of securing participants' privacy, the separation of data from identifiers, and protocols for using locked offices, filing cabinets, and password-protected files to avoid unauthorized use of participant data. The study team will meet regularly to discuss protocols for maintaining participants' privacy. The study team will also follow institutional policies for requiring mandatory training in human subjects protection before conducting any study activities.

G. Participant Reimbursement

Reimbursement. We provide reimbursement for time and/or travel for assessments administered throughout the course of the study. For Aim 1, each participant will receive 110 Rand at baseline, 120 Rand at 6-months, 130 Rand at 12-months, and an additional 20 Rand for

confirmation of STI treatment; 100 Rand for time and travel for filling out assessments is also given to intervention participants. For Aim 3, each participant will be provided with 100 Rand.

H. Emergency Care and Insurance

We follow procedures described above for potential serious adverse events. We also link with psychiatric services if participants decompensate, although our behavioral intervention has a prevention focus and only includes participants below a clinical threshold range for distress.This study falls under the University of Cape Town's no fault insurance policy to cover injuries incurred in research not sponsored by a pharmaceutical company.

I. What Happens at the End of the Study?

We conduct community dissemination activities after the study by holding community meetings and disseminating findings in briefings at community sites. We also disseminate findings in one page policy briefs to stakeholders in addition to publishing and presenting at international conferences.

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