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**HIV Oral Pre-Exposure Prophylaxis (PrEP) Trails:
A Systematic Review and Systematic Ethics Appraisal**

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HIV ORAL PRE-EXPOSURE PROPHYLAXIS (PrEP) TRIALS:
A SYSTEMATIC REVIEW AND SYSTEMATIC ETHICS APPRAISAL

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies

In partial fulfillment of the requirements
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ABSTRACT

BACKGROUND. Pre-exposure prophylaxis (PrEP) is an experimental HIV prevention approach whereby antiretroviral pills are used *before* anticipated exposure. It is unclear how ethical considerations have been addressed by investigators. **METHODS.** A systematic review of PrEP controlled prospective studies was conducted. Pre-determined data items were extracted from registries, protocols, reports, and consent forms. Study characteristics, methods, and ethics considerations were synthesized. **RESULTS.** Among sixteen studies included, twelve involved resource-limited countries. Quality scores were generally high and overall risk of bias was low. Considerations for *social value* were the least reported whereas considerations for the *fair selection of study population* were the most reported. More ethics considerations tend to be reported with time. No meta-analysis was performed, as few data were available. **CONCLUSION.** As critical as clinical data generation is for scientific progress, ethics should be monitored and adequately reported, lest lack of consideration for key principles be uncovered after the facts.

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TABLE OF CONTENTS

1.0	ABBREVIATIONS	1
2.0	STATEMENT OF THE PROBLEM	2
3.0	BACKGROUND.....	3
3.1.	A modern plague named HIV/AIDS	3
3.2.	Modern bioethics.....	5
3.3.	HIV pre-exposure prophylaxis (PrEP)	8
3.4.	Relevance of thesis.....	11
4.0	OBJECTIVES	13
5.0	METHODS	13
5.1.	Systematic review question	13
5.2.	Eligibility criteria	14
5.3.	Information sources	15
5.4.	Search.....	15
5.5.	Study selection.....	17
5.6.	Data collection process.....	17
5.7.	Data items.....	18
5.8.	Quality assessment.....	27
5.9.	Additional analyses.....	29
5.10.	Synthesis of results.....	30
5.11.	Amendments to original protocol	31
6.0	RESULTS	32
6.1.	Study selection.....	32
6.2.	Data collection process.....	32
6.3.	Data analysis	33
6.4.	Quality assessment.....	55
6.5.	Additional analyses.....	58

6.6.	Synthesis of results.....	61
6.7.	Risk of bias assessment.....	64
7.0	DISCUSSION.....	65
7.1.	Discussion on Objective 1: identification of PrEP trials.....	65
7.2.	Discussion on Objective 2: methods in PrEP trials.....	72
7.3.	Discussion on Objective 3: ethics appraisal of PrEP trials.....	79
7.4.	Discussion on Objective 4: synthesis of evidence.....	96
7.5.	Challenges & limitations.....	97
8.0	CONCLUSION.....	103
9.0	DISSEMINATION.....	106
10.0	LIST OF ATTACHMENTS.....	107
	Attachment 1. Reviewer's Brochure.....	107
	Attachment 2. Data Extraction Form.....	107
	Attachment 3. PrEP Ethics 101 Checklist.....	107
	Attachment 4. Consent Content Analysis Form.....	107
11.0	TABLES.....	108
	Table 1. List of studies included in the review (16 studies).....	108
	Table 2. Reported reasons for premature closures (4 studies).....	109
	Table 3. HIV oral PrEP trials' host countries (16 studies).....	110
	Table 4. Design features of HIV oral PrEP trials (16 studies).....	111
	Table 5. Eligibility criteria for HIV exposure (15 studies).....	112
	Table 6. Primary questions and phases of studies (16 trials).....	113
	Table 7. Main sources of financial or in-kind support (16 studies).....	114
	Table 8. Follow-up characteristics (15 studies).....	115
	Table 9. HIV detection features (15 studies).....	116
	Table 10. Number of trials reporting each ethics checklist item (14 studies).....	117
	Table 11. Exploring heterogeneity: outliers in ethics appraisal.....	123
	Table 12. Risk of bias analysis at study level (15 studies).....	124
	Table 13. Risk of bias analysis at outcome level (15 studies).....	124
12.0	FIGURES.....	125
	Figure 1. Study selection flow diagram.....	125

Figure 2.	World map of countries considered for hosting PrEP trials.....	126
Figure 3.	Primary analysis: ethics appraisal (14 studies).....	127
Figure 4.	Primary analysis: variations in ethics sub-scores & time trends (14 trials)	128
Figure 5.	Sub-group analyses: quality scores (15 trials).....	129
Figure 6.	Sub-group analysis: studies with 3-4 sources (11 studies).....	130
Figure 7.	Sub-group analysis: studies outside of the USA (10 studies)	131
Figure 8.	Sub-group analysis: efficacy/effectiveness as a primary question (9 studies)	132
Figure 9.	Sub-group analysis: study sites closed early (4 studies)	133
Figure 10.	Correlation ethics scores – Jadad scores (14 studies)	134
Figure 11.	Synthesis: time trends for ethics scores and Jadad scores	135
Figure 12.	Synthesis: past, current, and planned HIV oral PrEP trials	136
13.0	OTHER APPENDICES	137
Appendix 1.	Search strategies	137
Appendix 2.	List of key informants contacted	142
Appendix 3.	Ethics guidance documents screened	143
Appendix 4.	Reference documents for ethical analysis framework.....	144
Appendix 5.	Emanuel et al.'s ethical principles and benchmarks	145
Appendix 6.	"Modified" Jadad 5 point-scale.....	147
Appendix 7.	Other reviews of HIV oral PrEP trials.....	148
Appendix 8.	HIV oral PrEP trials mentioned in previous reviews.....	151
Appendix 9.	Hypothetical validation process for ethics checklist	152
Appendix 10.	Glossary.....	154
14.0	REFERENCE LIST	156

1.0 ABBREVIATIONS

AIDS	acquired immuno-deficiency syndrome
AST	aspartamine aminotransferase
CASI	computer-assisted self-interview
DMC	data monitoring committee
DSMB	data safety and monitoring board
FTC	emtricitabine
GGT	glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC ₅₀	concentration needed to reduce population growth of HIV by 50%, in vitro
IOM	<i>Institute of Medicine</i>
IQR	interquartile range
ml	millimetre
ng	nanogram (10 ⁻⁹ g)
NIH	United States National Institutes of Health
NVP	nevirapine
PI	principal investigator
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RCT	randomized clinical trial
TDF	tenofovir disoproxil fumarate
IU/l	international unit per litre
UNAIDS	Joint United Nations Programme on HIV and AIDS
USA	United States of America
WHO	World Health Organization

2.0 STATEMENT OF THE PROBLEM

HIV prevention research includes trials using antiretrovirals *before* an anticipated exposure, for persons considered at higher risk. This experimental approach is called pre-exposure prophylaxis or PrEP. *"Given (...) the potentially universal benefits of effective biomedical HIV prevention tools, there is an ethical imperative for global support to develop these modalities"*¹. And several research teams have undertaken to scientifically demonstrate the clinical value of HIV oral PrEP. But that endeavour presents considerable methodological challenges. Concerns have been expressed by the public about HIV oral PrEP trials conducted in developing countries, on bioethics grounds. This led to the premature closure of several study sites and caused many passionate comments to be made by scientists as well as by non-scientists. Yet, more recently, HIV oral PrEP has been receiving increasing support from different affected groups, including some community-based organizations. It is unclear whether ethical issues expressed some years ago were real or perceived, and how ethics challenges have been addressed by involved investigators.

3.0 BACKGROUND

3.1. A MODERN PLAGUE NAMED HIV/AIDS

Over 25 years after the initial outbreak of HIV/AIDS, there is still no cure, despite continuous and strenuous research initiatives. Recent epidemiological studies estimated that “[s]ince the beginning of the epidemic, 25 million people have died of HIV-related causes”, and that about 33 million adults and children were living with HIV in 2007, worldwide. That same year, 2.7 million people acquired the infection and 2 million people died of HIV/AIDS². The development and implementation of highly active antiretroviral therapies (HAART) helped maintain health and prolong life of persons living with HIV³, but patients on treatment can be subject to episodic disabilities⁴. Their quality of life may be affected by the side effects of the drugs, and they also may be stigmatized⁵. Besides, despite efforts towards universal access to treatment, many people in the areas of highest prevalence have no appropriate access to antiretroviral therapy. It was estimated that “for every one person who starts taking antiretroviral drugs, another three become infected”⁶.

There are three modes of HIV transmission: sexual, blood-borne, and vertical (parent-to-child)⁷. Some preventive methods are known to be effective against HIV acquisition. Behavioural prevention approaches related to sexual HIV transmission are summarized as the “ABC”⁸: *Abstain, Be faithful, Condomize*⁹. Behavioural harm-reduction standards for injecting drug users include the use of clean injection equipment and the avoidance of shared - potentially contaminated - equipment. Biomedical prevention approaches comprise male circumcision¹⁰⁻¹³ (for sexual transmission); universal precautions in clinical care/clinical research settings (i.e., standard infection control procedures: for blood-borne transmission); and antiretroviral therapy for pregnant women living with HIV and for infants born to them (for vertical transmission). Post-exposure prophylaxis, an HIV antiretroviral regimen, can also prevent infection, if implemented soon after a suspected infectious exposure (e.g., after occupational needle perforation or after sexual assault). Unfortunately, those strategies have not been sufficient to contain the epidemic. The reasons are diverse and complex, and include stigma and gender inequities¹⁴. Peter Piot, the former Executive Director of the United Nations Joint Programme on HIV/AIDS (UNAIDS), had declared that “[a]ddressing the prevention challenge will remain a top priority for UNAIDS in 2008 and beyond”⁶, thus supporting HIV prevention research initiatives.

Conducted in parallel with ongoing behavioural research, biomedical research to prevent HIV transmission can be classified into two groups: initiatives testing interventions to *reduce infectiousness* - targeting HIV positive persons - and initiatives testing interventions to *reduce susceptibility* - targeting HIV negative persons -. Experimental biomedical interventions to reduce infectiousness include the control of non-HIV sexually

transmitted diseases, therapeutic vaccines, and antiretroviral therapy for index partners within serodiscordant couples (couples in which one partner is HIV seronegative and the other is HIV infected). Experimental biomedical interventions to reduce susceptibility to HIV include the control of non-HIV sexually transmitted diseases, prophylactic vaccines, topical microbicides, cervical barriers (e.g., diaphragms, vaginal rings, sponges), and **antiretroviral pre-exposure prophylaxis**¹⁵.

HIV extensive antigenic variability, the uncertainty regarding correlations between immune responses and protection, and the lack of an ideal animal model for pre-clinical tests represent considerable challenges in HIV prevention research¹⁶. In the last decade, the world witnessed disappointing results from some HIV biomedical prevention trials, which affected the public's and the funders' confidence. In the area of microbicide research, nonoxynol-9, an over-the-counter spermicide, was showed to increase the risk for HIV infection¹⁷. That risk was associated with a higher risk for vulvo-vaginal irritation, especially with more frequent product use, which might increase susceptibility to infection¹⁸⁻²⁰. Harmful effects of cellulose-sulphate, an experimental microbicidal agent, were also observed. This led to the early closure of a trial after an interim safety analysis, in 2007²¹. That same year, vaccine research also experienced a significant setback with the early termination of Merck's STEP trial²². In that case, again, more seroconversions occurred in the intervention group than in the placebo group -especially in uncircumcised men immune to Ad5 -²³. It is probable that immune activation, a result of prior immunity to the Ad5 component of the vaccine, may itself have predisposed to HIV transmission²⁴. Also, in that trial, the guest antigens were non-surface, and the recombinant guest antigens were of clade B HIV (most prevalent clade in the USA) although they were tested in Africa, where clade C HIV is most prevalent²⁵. More recently, an advanced trial involving serodiscordant couples showed that acyclovir, commonly used to suppress herpes simplex virus-2 (the most common cause of genital herpes)²⁶, does not reduce the risk of HIV transmission when taken by seropositive partners infected with both HIV and HSV-2²⁷.

3.2. MODERN BIOETHICS

Ethics are “the discipline describing the behaviours, practices, thinking, and moral values that are generally agreed to be acceptable in society”²⁸. “Morality is the right or wrong (or otherwise) of an action, a way of life or a decision, while ethics is the study of such standards as we use or propose to judge such things (...). As a result, ethics is sometimes called **moral philosophy**.”²⁹ Sub-branches of ethics include **applied ethics**, which is “a term used to describe attempts to use philosophical methods to identify the morally correct course of action in various fields of human life.”³⁰ In the category of applied ethics, “[b]ioethics is the philosophical study of the ethical controversies brought about by advances in biology and medicine.”³¹

Instruments developed to serve as **bioethics guidelines** usually consist of a list of issues to consider when conducting or analyzing research involving human subjects, sometimes with practical recommendations and/or examples. Their core *raison d'être* is to insure the physical, psychological and social integrity of human subjects involved in research. Virtually all current bioethics guidance documents were somewhat inspired by a seminal code developed right after World War II and its historical *Nuremberg Doctors Trial*. That trial judged Nazi medical doctors for atrocities committed both on civilians (essentially ethnic minorities) and on war prisoners, under the guise of scientific experimentation³². Those atrocities included exposure to extreme cold or pressure, forced sterilization, deliberate infection, and massive killings. The Court of Law's conclusion was a strong and formal blame of the doctors' wrongdoing. The ensuing publication of the *Nuremberg Code*, in 1947, is a landmark in contemporary biomedical research ethics. The ten statements of this *legal document* underline the importance of voluntary consent, risk-benefit evaluation, and scientific justification, in clinical research³³.

An official policy of the World Medical Association, the *Declaration of Helsinki*, was also motivated by the Nuremberg Doctors Trial and had initially 14 statements (1964)³⁴. The current version (2008) has 35 *statements* that cover health and rights of human/animal subjects, involvement of underrepresented populations in research, scientific rigor, ethical/legal/regulatory standards, respect for the environment, requirements regarding research protocols, ongoing risk-benefit assessment, trial registration, free informed consent/assent of competent subjects and proxy consent, privacy and confidentiality, information disclosure to participants, prevention of coercion, requirements for research publication, distinction between medical care and medical research, appropriate controls, and benefits after study closure³⁵.

Another influential and commonly cited ethics guidance document is the United States National Commission's *Belmont Report* (1979)³⁶. Among other research-related scandals reported in news media in the early 1970s, the Tuskegee study and the public outrage it caused played a big role in the creation of the National Commission and in the development of the Belmont Report. The Tuskegee project refers to an observational

study conducted between 1932 and 1972 by medical doctors, in Alabama, USA. That study enrolled low educated, resource-limited Black males and aimed to describe the natural history of syphilis, a sexually transmitted disease. Consent was not sought from those subjects and they were neither informed about nor provided standard of care, even when they developed serious complications (e.g., blindness, dementia). Furthermore, the study procedures were maintained despite the availability of penicillin, proved efficient in 1942, and after the publication of the Declaration of Helsinki (1964)³⁷. The Belmont Report is an analytic framework presenting 3 *moral principles (respect for persons, beneficence and justice)* proposed as a basis for the fulfillment of practical responsibilities of researchers (informed consent, risk-benefit assessment, and selection of participants)³⁸.

Many other ethics guidance documents are now available and are sometimes enforced in regulations or laws. The *International Compilation of Human Research Protection* lists about “1,100 laws, regulations, and guidelines that govern human subjects research in 92 countries, as well as standards from a number of international and regional organizations.”³⁹ This plethora and diversity of ethics guidelines can be explained by the specificity of some ethical challenges based on the discipline, and by the need to adjust to evolving and context-dependent ethical perspectives. For instance, more and more clinical trials are conducted in developing countries by researchers from richer countries⁴⁰. In order to address concerns about potential exploitation in this context, the United States' National Bioethics Advisory Commission published two reports entitled *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001)^{41, 42}. And the Council for International Organizations of Medical Sciences (CIOMS), jointly created by two agencies of the United Nations Organization, proposed a living guidance document: *International Ethical guidelines for Epidemiological Studies* (1993, last update in 2008)⁴³.

HIV research has its own challenges and specificities. John Killen wrote that “[t]he epidemic has (...) had a profound impact on virtually every facet of research ethics”. He discussed, for instance, “how activism and other events in the early history of the HIV epidemic in the United States have caused the field to look anew at the principles of autonomy and justice, as they were articulated in the Belmont Report and implemented in regulation and policy that followed from it.”⁴⁴ He added that “[t]his legacy is clearly etched in sweeping U.S. regulatory reform regarding human experimentation in the case of treatments for life-threatening conditions and in the processes of ethical review of clinical research that is integral to research and development of new therapy for them.”⁴⁴

In discussing and appraising bioethics, principle-based guidelines are frequently used as references, as they may be more convenient for structured analyses. In biomedical research, Beauchamp and Childress's principles (*beneficence, non maleficence, justice and autonomy*) are commonly considered “pillars” - at least in Northern America -. First proposed in the 1970s, these principles were last updated in 2008⁴⁵. However, ethics

principles vary in name, in number, and in description, depending on the guidelines, and even depending on the version of a particular guidance document. As an example, the Canadian *Tri-Council Policy Statement* is in the process of formulating three principles (*concern for welfare, respect for autonomy, respect for the equal moral status of all humans*)⁴⁶ whereas its previous version had eight principles (*respect for human dignity, respect for free and informed consent, respect for vulnerable persons, respect for privacy and confidentiality, respect for justice and inclusiveness, balancing harm and benefits, minimizing harm, maximizing benefit*)⁴⁷.

Most ethics guidelines simply list principles, recommendations or statements whereas some give more weight to particular issues. For instance, recommendations proposed in *Ethical Issues in International Research: Trials in Developing Countries* explicitly present voluntary informed consent as “*the substantive ethical standard*”⁴². Other authors have also singled out critical difficulties in obtaining true voluntary informed consent in international research. Indeed, designing an adequate consent form can be particularly arduous due to the challenging task of providing comprehensive information in a language prospect participants can understand, and due to the cultural aspects of consent documentation⁴⁸. However, although informed consent is most often necessary, it is never sufficient to make clinical research ethical. For some, this common focus on informed consent “*reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics*.”⁴⁹ Besides, even within industrialized countries, true informed consent may be difficult to warrant⁵⁰, voluntariness of consent may be questioned⁵¹, volunteer participants may not understand the distinction between medical research and medical treatment⁵², the language of consent forms may be hardly accessible to candidate participants⁵³, and potential participants might experience angst⁵⁴ and hesitation to sign a consent form typically presented based on a “*legalistic approach*”⁵⁵.

When designing, conducting or analyzing research, it is essential to use ethics guidelines that most properly fit the research area in question, and that have the most suitable degree of specificity. But it is also important to interpret ethics recommendations in context, and to make reasonable adjustments to ethics guidelines, as deemed appropriate. “*Ultimately, a thoughtful process of balancing ethical considerations can be as important as any particular judgment in the effort to ensure that research is conducted ethically*”⁵⁶.

3.3. HIV PRE-EXPOSURE PROPHYLAXIS (PREP)

HIV antiretrovirals are chemical compounds specifically used for the treatment of *acquired* HIV infection. Although they do not cure the infection, they can suppress the replication of the virus in the body, and thus slow down the progression towards AIDS (the acquired immunodeficiency syndrome) and death. Also, by reducing the viral load (number of viral particles circulating in the body) in persons on treatment, antiretrovirals help reduce infectiousness, and so, they reduce HIV transmissibility^{57, 58}.

Pre-exposure prophylaxis (PrEP) is *“a novel approach to HIV prevention research whereby seronegative participants considered as highly exposed to the virus take antiretrovirals, to reduce the likelihood of HIV infection”*⁵⁹. It is hoped that, by having an optimum level of such drugs in their system before exposure to the HIV, people at higher risk would be protected from becoming infected. Although PrEP is “new” in HIV prevention, the concept itself is not. Indeed, pre-exposure prophylaxis is the basis for immunizations, for malaria prevention in travellers, and for the prevention of undesired pregnancy, for example.

Following encouraging results from studies testing PrEP in animals⁶⁰⁻⁶⁵, and with a pressing need for a greater variety of HIV prevention options, some HIV oral PrEP clinical trials have been conducted in humans, raising great hopes in the scientific community⁶⁶. For instance, based on a mathematical model, Ume Abbas has concluded that PrEP could potentially *“avert more than 3 million new HIV-1 infections in sub-Saharan Africa over 10 years”*⁶⁷. Other models also predict positive effects of PrEP^{68, 69}. And Nancy Padian stated that *“[i]f proven safe and effective, this approach might be more user-friendly because it could be delivered independently of sexual practices and other risk behaviours, either daily or intermittently to coincide with planned sexual intercourse”*⁷⁰.

Nonetheless, HIV oral PrEP studies also raised concerns in developing nations that hosted such trials. In these countries, some trials have been the object of much argument, relayed by local and international news media, between advocacy groups and scientists⁷¹. Reported concerns include a lack of community involvement in the planning of the trials, doubts on the quality of treatment provided to seroconverting participants, and worries about the quality and duration of medical care to be provided after the trial⁷². In Cambodia, where a study was halted in 2004, reported reservations related to the study's effects on the human rights of the Cambodian people, the use of commercial sex workers from a poor country for experimental drug testing, the use of a placebo as control, and the quality of HIV prevention counselling to participants⁷². In Cameroon, where a study site closed in 2005, there were fears that there would be no medical care for participants who would become HIV positive during the trial period, that the study population was not sufficiently informed of the risks involved in participating in the trial, that the number of study support staff was inadequate, that participants were being

exploited and treated like “guinea pigs”, and that the study aimed at promoting the commercial prospects of the manufacturer of tenofovir (i.e., Gilead Sciences, Inc.)⁷².

However, *“investigators claim that the tenofovir PrEP trials were developed collaboratively with the host countries to meet relevant ethical standards. In West Africa, formative research studies with the community of participants helped to design the informed-consent instrument, to identify the preferred sites of receiving health care, and to identify sources of stigma, which the investigators tried to reduce”*⁷³. In response to the early termination of HIV oral PrEP trials, some scientists commented on the role played by advocacy groups. Peter Hammer and Tammy Lundstrom (2005) wrote, about the trial in Cambodia, that *“a well intentioned and well designed research proposal reached an impasse that led to its cancellation”*⁷⁴. Singh (2005) argued that *“[if] tenofovir is someday proven to be clinically efficacious as a [PrEP], (...) irresponsible reporting and activism surrounding tenofovir could cause those in need to snub the drug if, or when, it becomes licensed for use as a [PrEP]”*⁷³. And Mills (2006) warned that *“[d]isappointments stemming from media hype and misinterpretation of early trials can make policy and recruitment of appropriate trial populations difficult”*⁷⁵.

Ethical issues in HIV oral PrEP, whether real or perceived by stakeholders, can challenge the planning and conduct of the studies, as well as their scientific validity. And, as others have pointed out, *“(...)scientifically unsound research on human subjects is ipso facto unethical”*⁴³. Therefore, it is essential to examine both methodologies (scientific validity) and ethical considerations, to draw any conclusion on the ethical evaluation of HIV oral PrEP trials. Trials’ premature closures appeared to result from public pressure and/or political decisions, not from a decision from investigators, a Data Monitoring Committee, or a sponsor, as it is commonly the case. This deserves attention and consideration.

HIV oral PrEP is ethically challenging because it is outstanding in at least four aspects that all may affect theoretical and practical methodologies. **First, HIV is a very versatile virus.** Despite many breakthroughs since its discovery, it is still not fully understood. HIV has two known types (1 and 2), several identified sub-types, and even circulating recombinant forms (transmissible genetic hybrids of different types or sub-types). HIV genotypic variants have different geographical distributions and different chemical and biological characteristics²⁵. Such a complexity can influence the transmissibility, the sensitivity of the diagnostic tests, the pharmacological efficacy/harm of the treatments, and the clinical progression of the infection²⁵.

Second, PrEP trials require exposure to HIV. As other HIV prevention trials, they entail, to allow

conclusions on efficacy, that healthy subjects be initially non-HIV infected then be exposed to the virus, for the purpose of scientific validity. So, the most serious risk in participating - although related to pre-existing risk - is a potentially lethal one. HIV infection can indeed lead to AIDS (the acquired immuno-deficiency syndrome) and eventually death - in the absence of a lifelong treatment -. Moreover, although prevention trials in humans must be backed up and preceded by sufficient pre-clinical studies, there is always a chance that the drugs tested in HIV oral PrEP trials may truly have no or only a partial protective effect and/or unexpected adverse effects. So, the greatest care must be given to provide the standard for HIV prevention to all participants enrolled⁷¹ while still enabling the experiment. Indeed, it would be ethically unacceptable to test HIV oral PrEP against a placebo control - unless there was absolutely no valid alternative preventive intervention and/or true clinical equipoise - ^{35, 76}. If a tested product does not provide the protection hoped for, one also needs to consider provision of care to those infected during the study and/or some kind of compensation, after the trial.

Third, study populations will likely be vulnerable. Study subjects will ideally be individuals highly exposed to HIV and, incidentally, such persons usually may fit the definition of vulnerable populations, in a way or another. *“Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests”* (CIOMS 2008, Commentary on Guideline 13)⁴³. Key populations at higher risk of HIV exposure include sex workers, men having sex with men, and injecting drug users. However, HIV infection risk is not less real for persons who do not belong to those groups. For example, any unprotected heterosexuals contact or unsafe medico/surgical practices may also represent exposures. In any case, with vulnerable persons as study participants, the risk of exploitation might be increased.

Fourth, PreP research relies on the involvement of resource-limited settings. At least some HIV oral PrEP trials have been conducted in low and middle income countries by scientists from industrialized countries. Between sponsoring nations and host countries, there can be huge differences in the language, the culture, the belief system, the needs, the resources, the ethical perspectives on research, the medical system, the accessibility to care, the medical standards of care, and health-related regulations and laws.

3.4. RELEVANCE OF THESIS

Although HIV oral PrEP has been extensively discussed either positively or negatively by many authors, both scientists and non scientists, in high impact peer-reviewed journals as well as on internet blogs, reports have given limited description of the trials. Only one recent systematic review is available, in the Cochrane Library, which focused on safety and efficacy⁷⁷. However, the PrEP research field is still too new and data are too limited. In fact, the Cochrane review could include only one study and no metanalysis was performed.

After HIV oral PrEP study sites were closed in Cambodia (2004) and Cameroon (2005), the ethical debate over this approach continued within the scientific community. Involved stakeholders had rounds of discussions and consultations to determine what had gone wrong and how to adjust their methods to allow HIV oral PrEP research to go on^{78, 79}. For instance, a committee was formed by the Institute of Medicine, in order to identify methodological challenges and to make recommendations for future directions¹⁵. However, it clearly reports that it had *not* in its mandate to analyze ethical issues not directly related to internal validity. This committee was sponsored by the *Bill and Melinda Gates Foundation*, a PrEP research funder⁸⁰, and the methodological challenges were identified based on a literature review and consultations of experts¹⁵.

A more detailed and systematic description of HIV oral PrEP trials features may allow for a more balanced ethical appraisal of this experimental approach. At this point, relying solely on reports is limiting. And surveying involved stakeholders, although greatly informative, might yield biased data (social desirability), considering the sensitivity of the issues and past controversies. This thesis presents a systematic analysis of the HIV oral PrEP trials, based on trial registry files, study reports, study protocols and consent forms.

Trial registries have been established a few years ago as a public catalogue of clinical studies. The intent was to enhance transparency in reporting scientific research, to prevent duplication of research, and to minimize publication bias, by posting information on clinical studies at different stages (e.g., in planning, on-going), before their results are published⁸¹. Hence, nowadays, more and more trials are registered. Study reports are very commonly used, usually by science-literate persons, as a means to get informed on the results of completed studies. It was expected, in the case of HIV oral PrEP research, that few reports would be available; and editors may restrict the length of the text to certain limits that, sometimes, do not allow for methodology to be extensively detailed. On the other hand, protocols usually have detailed background justifications and methodologies, to support the relevance of a proposed trial. Protocols are to reflect how researchers intend to proceed; what scientific, ethical or operational challenges/issues they expect; and how they are to address those. A protocol is also a key scientific document that needs to be approved by an ethics committee before a trial can start enrolling human participants. As for the consent form, it is the main document that describes the

study to prospected participants and that will be the basis for their decision to get enrolled or not.

Apart from study reports, aforementioned target documents are seldom used to appraise clinical studies but they were deemed to be particularly relevant for this work. My thesis will complement past contributions to the body of literature on HIV oral PrEP research and ethics. It is original in that such an analysis has never been conducted and that the review sought to include all trials, irrespective of their status. It is based on empirical data, and was designed and conducted independently from stakeholders supporting or disapproving of HIV oral PrEP research. The methodology and results of this work will not only contribute to better understand challenges in HIV oral PrEP research but may also be relevant for other fields of clinical research, particularly - but not limited to - research in developing countries.

4.0 OBJECTIVES

The primary objectives of this thesis were:

- 1) to identify all past, current, and planned HIV oral PrEP trials, worldwide
- 2) to present a descriptive synthesis of HIV oral PrEP trials' methods; and
- 3) to perform an ethics appraisal of HIV oral PrEP trials.

A secondary objective was:

- 4) to synthesize the evidence for efficacy and safety of HIV oral PrEP, in humans.

5.0 METHODS

This review was based on a protocol, as per the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA Statement: upgrade of the QUORUM Statement)⁸². The protocol was not registered but is available upon request. A *Reviewer's Brochure* was developed to serve as a reference for assessors, who were formally trained to follow standard review procedures ([Attachment 1](#)). Reviewers were not blinded to studies' identifiers for any phase of the review.

5.1. SYSTEMATIC REVIEW QUESTION

How have ethics-related methodological challenges been addressed in HIV prevention prospective controlled trials testing oral HIV antiretrovirals versus placebo or any other comparator, and measuring seroconversions and adverse events, in sexually active HIV seronegative humans?

After the classic PICOS framing scheme⁸³, the study question was structured as follows: P(population)= sexually active HIV seronegative humans; I(intervention)= any oral HIV antiretroviral regimen; C(comparator)= any type of comparator (e.g., placebo, other active intervention, no intervention); O(outcomes)= HIV infection (at least seroconversions), adverse events (physical/physiological and/or psychosocial); S(study design)= any prospective controlled trial. The structured question defined the eligibility criteria.

5.2. ELIGIBILITY CRITERIA

No language restriction was applied. Eligibility criteria defined above were based on the arguments below.

POPULATION. In humans, there are 3 routes for HIV transmission: sexual, blood-borne, and vertical (parent-to-child)⁷. Sexual intercourse is the most common transmission mode for HIV infection, globally, hence the focus on sexually active persons⁷. Populations at higher risk include adolescents² so, no restriction was set for age. However, vertical transmission was excluded because HIV antiretrovirals are already known to be effective to prevent mother-to-child transmission⁸⁴.

INTERVENTION. Several HIV oral antiretrovirals could be good potential candidates for HIV oral PrEP⁸⁵. So, this review did not target particular antiretrovirals. However, it was restricted to antiretroviral already approved for commercial distribution and treatment prescription because, typically, experimental HIV antiretroviral agents are first tested for therapeutic use. Also, I excluded trials testing “topical PrEP”, that is, antiretroviral-based topical agents. Such products are not yet approved, and topical administration involves some challenges and mechanisms of action different from oral antiretrovirals. Such agents are usually considered as “second-generation microbicides”, a distinct experimental approach in HIV biomedical prevention.

COMPARATOR. Although placebo-controlled trials were expected, other controls might have been considered (e.g., other active intervention, or no intervention), especially for studies not focusing on efficacy/effectiveness. Studies with no control group (e.g., observational studies) were deemed to be too prone to bias for the kind of appraisal intended and were hence excluded.

OUTCOMES. In the absence of a valid surrogate outcome measure for new HIV infection, seroconversion is the only clinically relevant measure for assessing efficacy of a preventative intervention¹⁵. And, in the context of HIV biomedical prevention research, relevant adverse events include not only physical/physiological harm (e.g., laboratory abnormalities and clinical signs/symptoms) but also psychological harm (e.g., anxiety related to HIV testing, decreased use of condoms) and social harm (e.g., relational issues with partner).

STUDY DESIGN. Randomized trials are considered the most valid way to demonstrate a causal relationship between a tested intervention and a pre-specified endpoint⁸⁶. Although quasi-experimental (i.e., non randomized) trials are more prone to bias, they can still provide some sense of causality, as they are prospective and have one or more comparison group(s). Because they don't have those key features, retrospective and uncontrolled studies were excluded. Early phase clinical studies (e.g., pharmacokinetics, pharmacodynamics) were considered irrelevant unless they featured one or more control group and were clearly described as exploring HIV pre-exposure prophylaxis.

5.3. INFORMATION SOURCES

In order to identify and locate HIV oral PrEP trials, 4 types of information sources were used: the *World Wide Web*, clinical trial registries, electronic databases, and key informants. Conference proceedings and abstracts were not searched because they usually report experts' opinions or partial study results. It was felt that such sources would not add to this review.

5.4. SEARCH

All searches were periodically updated; dates of most recent searches are indicated in paragraphs below. Search strategies are presented in Appendix 1.

WORLD WIDE WEB

An exploratory review on the *World Wide Web* - using *Google* main search engine - identified three relevant specialized websites. The *PrEP Watch* website (www.prepwatch.org; now moved to www.avac.org) is dedicated to monitor advances in HIV pre-exposure prophylaxis research. It presents a *Table of Trials* that is updated about quarterly (last screen on 29 July 2009: June 2009 version)⁸⁷. Two other specialized websites that post lists of HIV biomedical prevention trials were identified. These are: the *Microbicides Trials Network* website (www.mtnstopshiv.org; last screen on 2 July 2009) and the *HIV Prevention Trials Network* (www.hptn.com; last screen on 2 July 2009). The *World Wide Web* "at large" was also searched, using a fixed combination of key words and the *Google* main search engine (www.google.com; last screen on 2 August 2009).

TRIAL REGISTRIES

Clinical trial registries were searched using search functions and/or keywords, since registries do not have a controlled vocabulary. Initial searches were done in the United States National Health Institutes (NIH) clinical trials registry (www.clinicaltrials.gov; last search on 5 July 2009). Searches were also run in the *MetaRegister of Controlled Trials* (www.controlled-trials.com/mrct; last search on 5 July 2009) and in the World Health Organization's *International Clinical Trial Registry Platform* (www.who.int/ictrp/en; 10 February 2009). The

latter two registries actually combine information from multiple registries and search options and/or outputs allow for the identification of registries of origin. So, registries deemed irrelevant (e.g., *Leukaemia Research Fund*) or redundant (e.g., US National Institute of Health) were excluded ([Appendix 1](#)).

KEY INFORMANTS

A contact list of investigators and sponsors involved in HIV oral PrEP research was developed, based on the information collected from the trial registries ("Contacts" and/or "Investigators" field-s). The principal investigator(s) and/or the person(s) identified as contact(s) were first contacted by email, using a common template message. Follow-ups were done by email, fax and/or phone, as needed. Investigators were explained the thesis project and were requested copies of the latest version of their approved study protocols and consent forms. They were offered the option to receive a copy of my systematic review protocol and were given the opportunity to ask questions about it. The choice of documents requested was informed by details found on trial registries, as the latter include trial status as well as trial start and end dates. For instance, unpublished study results were not requested for a trial that was labelled as on-going. Communications with investigators were not made if full source documents were found on the *World Wide Web*. Communications with identified sponsors were deemed unnecessary when study-related documents could be obtained from principal investigators. The list of key informants contacted is presented in [Appendix 2](#).

ELECTRONIC DATABASES

For the retrieval of primary reports, 3 electronic databases were searched, using structured strategies including controlled vocabulary. In the *OvidSP* interface, a search strategy was developed, embedding the Dickersin filter for randomized trials⁸⁸, for *Medline* and *Medline In-Process* (last search: 1950 to January Week 4 2009). That search strategy was adapted to *Embase* (last search: 1980 to 2009 Week 06), using the SIGN filter for randomized trials⁸⁹, and to the *Cochrane Central Register of Controlled Trials* (last search: 4th Quarter 2008).

5.5. STUDY SELECTION

Search outputs were independently screened by two reviewers. Outputs from the **trial registry/World Wide Web** searches were screened based primarily on study titles/weblink title and, secondarily, on the detailed description of each potentially eligible study. Duplicates from trial registries/World Wide Web were identified using information found in alternate sources, or through direct communication with key informants. Outputs from the **electronic database** searches were imported into a *Reference Manager*® file (*The Thomson Corporation*, version 11) where they were cleaned from duplicates. Deduped outputs from electronic database searches were screened based primarily on study titles and, secondarily, on the abstracts of each potentially eligible study. Selection was based on the eligibility criteria defined above: Population=sexually active HIV seronegative humans; Intervention=any oral HIV antiretroviral regimen; Comparator=placebo or any other control; Outcomes=to include HIV seroconversions and adverse events; Study design=prospective controlled studies. Sub-studies that had a distinct protocol were not individually analyzed (excluded as duplicates).

5.6. DATA COLLECTION PROCESS

Trial registry files were copied and saved in *Microsoft Word*® format (Microsoft, Inc., version 2003). Full protocols and consent forms posted on specialized websites (www.prepwatch.org, www.hptn.org, www.mtnstopshiv.org) were downloaded and electronically saved. Clinical study reports were also downloaded from the *World Wide Web* and electronically saved. Involved investigators or sponsors were contacted for the acquisition of protocols and consent forms that were not found online. I attended some major HIV/AIDS fora and conferences (2008-2009) and/or I screened their communications, for updates on HIV oral PrEP research.

5.7. DATA ITEMS

I developed a set of extraction forms to capture pre-defined data items. A standardized *Data Extraction Form* included 8 sections, for: 1) study identification, 2) verification of eligibility criteria, 3) study timeline and settings, 4) material and structural support, 5) data source documents, 6) scientific and clinical methods, 7) results, and 8) quality assessment. I also developed an ethics appraisal checklist, with 8 domains representing 8 ethics principles. The development process of this checklist is presented below (section 5.7, *Objective 3: ethics appraisal of PrEP trials*). Both forms were piloted on two of the included studies and were amended to optimize the extraction process. Data items of interest were cross-referenced by source document and source document page/paragraph, in order to facilitate accuracy checks and conciliation between independent reviewers.

Key data items were extracted from 4 main categories of source documents: study reports, consent forms, study protocols, and trial registry files. Following that same order, a precedence rule was defined, to decide on the source to favour, should there be inconsistencies across source documents, for the same included study. An inconsistency was defined as a pair of mutually exclusive statements related to the same data item. Complementary information was not considered an inconsistency. Also, in case of a missing source document, data items were to be searched in and extracted from the next document available, based on this precedence rule. Investigators were not surveyed nor were they queried for clarifications on data items found or not found in source documents.

Once obtained, each source document was scanned independently by two reviewers, to confirm that studies selected fulfilled all eligibility criteria. Each source document retained was then fully reviewed (i.e., all sections of the text were read) by each reviewer, independently, for the extraction of pre-determined data items.

DATA ITEMS FOR OBJECTIVE 1: IDENTIFICATION OF PrEP TRIALS

Data items related to the identification of included trials were manually extracted onto the *Data Extraction Form* then electronically captured onto a customized *Microsoft Excel*® spreadsheet (Microsoft, Inc., version 2003). The *Excel*® file was used to facilitate data management and to run quantitative analyses (frequencies) on characteristics of studies included. The identity of lead investigators was determined based on trial registry files (“*Investigators*” field), protocol front pages (e.g., protocol chair/co-chair, study director, principal investigator), or reports (lead author). The country leading the research was determined based on the institution(s) to which the lead investigator(s) were reportedly affiliated. The main sources of material support were determined based on sponsors and in-kind providers reported as such. The *Data Extraction Form* is presented as Attachment 2.

DATA ITEMS FOR OBJECTIVE 2: METHODS IN PrEP TRIALS

Data items related to the methods used in included trials were manually extracted onto the *Data Extraction Form* then electronically captured onto the customized *Microsoft Excel*® spreadsheet (Microsoft, Inc., version 2003). For included studies that had an ineligible intervention (e.g., topical antiretroviral) as comparator, data extraction and analyses were limited to the eligible additional comparator (e.g., placebo). The *Excel*® file was used to facilitate data management and to run quantitative analyses (frequencies) on the methods of studies included. The analysis of HIV detection methods included, on top of the source documents’ text, the review of appendices displaying HIV detection algorithms, when those were given. That analysis was informed by WHO/UNAIDS *Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities*⁹⁰, and WHO’s training on *Testing Strategies and Algorithms*⁹¹. The *Data Extraction Form* is presented as Attachment 2.

DATA ITEMS FOR OBJECTIVE 3: ETHICS APPRAISAL OF PrEP TRIALS

Literature Review

I conducted an ancillary literature review to identify ethics guidance documents relevant to HIV oral PrEP. Eligible documents were to be 1) specific to HIV biomedical prevention research, 2) clearly structured (e.g., by ethics principles), 3) concise, and/or 4) applicable to transnational research/research conducted in resource-limited communities. I screened twenty documents ([Appendix 3](#)). Documents presenting generic guidance (e.g., Nuremberg Code), although relevant, were excluded as being non specific to HIV biomedical prevention research. Although all identified guidelines were informative, three documents were deemed most relevant and appropriate for the intended ethical appraisal of HIV oral PrEP trials. I used them to develop my ethics analytic framework. These three documents of reference are described in the following section.

Documents of Reference ([Appendix 4](#))

Document 1. The *Ethical Principles and Benchmarks for Multinational Clinical Research* were published by Ezekiel Emanuel *et al.*, in 2004⁹². Dr. Emanuel is a medical doctor and a well-established bioethicist⁹³. Based on previous literature and on a theoretical reflection, he and his co-authors proposed a framework to facilitate a systematic analysis of international clinical research, particularly for situations where scientists from developed countries do trials in developing ones. As mentioned above, some HIV oral PrEP trials have been conducted internationally, and Emanuel *et al.*'s guidelines have characteristics that can help capture ethical challenges relevant to such research. This framework features a list of eight principles and "[e]ach principle is specified by benchmarks that offer a specific elaboration and understanding of each principle" ([Appendix 5](#)).

A short description of their meaning, based on the original paper⁹², is given below:

- 1) *collaborative partnership*: local collaborators should be involved as equals
- 2) *social value*: study should be relevant to host community and its local health issues
- 3) *scientific validity*: methods proposed should be feasible and acceptable in host community
- 4) *fair selection of study population*: selection should be based on scientific validity and risk minimization
- 5) *favourable risk-benefit ratio*: foreseen benefits to participants should outweigh potential risks
- 6) *independent review*: ethics review should be transparent and done by competent persons

- 7) *informed consent*: consent process should be informed, free and culturally appropriate
- 8) *respect for recruited participants and study communities*: all participants should receive appropriate standard of care and relevant information in a timely fashion

In the view of the authors, “[t]hese eight principles are universal; they apply in all countries and contexts, regardless of sponsorship. The principles are general statements of value (...)”⁵⁶. Each of those principles is associated with a short inventory of benchmarks, 31 in total. This model is interesting because, as explained by its authors: “by specifying and clarifying the eight principles, these benchmarks should help to narrow any disagreement related to specific cases, making it easier to focus on the substance of the disagreement, assess the importance of the problems and concerns, and even identify potential solutions.”⁵⁶

Document 2. The guidance document on *Ethical Considerations in Biomedical HIV Prevention Research* was developed by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)¹. It “*highlights, from the perspective of UNAIDS and WHO, some of the critical ethical elements that must be considered during the development of safe and effective biomedical HIV prevention interventions*”. It “*incorporates (...) lessons learned in the field of biomedical HIV prevention research (...) including (...) antiretroviral pre-exposure prophylaxis.*”¹

UNAIDS is “*an innovative joint venture of the United Nations family, bringing together the efforts and resources of ten UN system organizations in the AIDS response to help the world prevent new HIV infections, care for people living with HIV, and mitigate the impact of the epidemic*”⁹⁴. WHO is “*the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends*”⁹⁵.

Both organizations are well-established and respected institutions, benefiting from the experience of working teams and partners that are representative and knowledgeable of many different countries (industrialized and developing). The development of the first version of these guidelines involved “*lawyers, activists, social scientists, ethicists, vaccine scientists, epidemiologists, nongovernmental organisation (NGO) representatives, people living with HIV, and people working in health policy from a total of 33 countries*”; the subsequent revision also involved international consultations of multidisciplinary experts^{1, 96}. This gives a broader ethical perspective to the guidelines that are *de facto* likely to be more culturally inclusive and culturally sensitive.

The document articulates nineteen guidance points, namely on 1) development of biomedical HIV prevention interventions; 2) community participation; 3) capacity building; 4) scientific and ethical review; 5) clinical trial

phases; 6) research protocols and study populations; 7) recruitment of participants; 8) vulnerable populations; 9) women; 10) children and adolescents; 11) potential harms; 12) benefits; 13) standard of prevention; 14) care and treatment; 15) control group; 16) informed consent; 17) monitoring informed consent and interventions; 18) confidentiality; and 19) availability of outcomes. Some of those points do match or resemble Emanuel *et al.*'s benchmarks. Contextual definitions and descriptions of ethics considerations were deemed to be more adequate in the UNAIDS document, though.

Document 3. The book entitled *Methodological Challenges in HIV biomedical prevention trials* was published in February 2008¹⁵. It is the report of a committee of the Institute of Medicine (IOM). "*This IOM Committee was formed at the request of the Bill and Melinda Gates Foundation and charged with addressing methodological challenges in late-stage nonvaccine trials with a specific focus on microbicide and pre-exposure prophylaxis*"¹⁵. Committee members convened workshops and meetings with principal investigators of trials of interest and "*other experts in HIV prevention*". They also reviewed the literature on methods issues related to HIV prevention trials, and they talked with research "*staff and study participants as well as community, government and research stakeholders*"¹⁵.

The report is organized in chapters that cover nine areas of methodological challenges: 1) basic design features: size, duration and type of trials, and choice of control group; 2) design considerations: risk-reduction counselling; 3) design considerations: pregnancy; 4) design considerations: adherence; 5) design considerations: recruitment and retention; 6) site preparedness; 7) estimating HIV incidence; 8) performing interim monitoring and analyzing trial results; and 9) alternative trial designs. The report lists a total of 43 recommendations to optimize the methodology of nonvaccine HIV biomedical prevention trials.

Other documents.

A fourth tool, UNAIDS/AVAC's *Good participatory practice - Guidelines for biomedical HIV prevention trials*⁹⁷, was also deemed of interest. It is to complement the *Ethical Considerations in Biomedical HIV prevention Research*¹. It was developed following recommendations from consultations on lessons learnt from trials halted in Cambodia and in Cameroon^{78, 79}. This document describes 10 core principles: 1) scientific and ethical integrity; 2) respect; 3) clarity in roles and responsibilities; 4) shared responsibility; 5) participatory management; 6) autonomy; 7) transparency; 8) standard of prevention; 9) access to care; and 10) building research literacy. The rest of the text proposes initiatives to consider in engaging local partners throughout biomedical HIV prevention trials. Although this is a valuable tool and a comprehensive resource, it was

deemed too technically detailed for the analysis intended.

Finally, the reports on *Ethics of International Research: Clinical Trials in Developing Countries* (volumes I and II)^{41, 42} were not used either. As for UNAIDS guidance documents, they are based on experts' consultations. In this case, consultations involved only USA stakeholders, which limits the generalizability of the recommendations. Like Emanuel et al.'s principles, they are applicable to transnational research although not specific to HIV biomedical prevention studies. But recommendations presented in those reports are less clearly structured and less systematic than Emanuel et al.'s model. And, except for policy-related guidance, most recommendations enunciated in those reports are addressed in at least one of the three documents retained above.

PrEP Ethics 101 Checklist (Attachment 3)

Based on the ancillary literature review mentioned above and on the three documents of reference selected, I developed a checklist of 101 ethical items. I did so in four steps:

- 1) **I fully reviewed papers published until 2008 that focused on HIV oral PrEP research.** These papers were identified through my ancillary search and included scientific articles (fact sheets, editorials, commentaries, study reports and reviews), media articles, and a previous ethics analysis of the PrEP trial in Cameroon⁷¹. I identified ethical issues and concerns that were reported and discussed, and I reformulated them as checklist items. This is how I developed my initial list.
- 2) **I fully reviewed UNAIDS's *Ethics Considerations in HIV Biomedical Prevention Trials* guidelines¹.** While reviewing that document, I extracted what appeared to me as the main conceptual recommendations. I formulated identified concepts as ethics items and I added them to my initial list.
- 3) **I fully reviewed the IOM's recommendations on *Methodological Challenges in Biomedical HIV Prevention Trials*¹⁵.** While reviewing those recommendations, I extracted what appeared to me as the main conceptual guidelines. I formulated identified concepts as ethics items and added them to my list.

After I revised my list and removed redundant statements, I was left with 101 items. Eighty-nine items were directly derived from the UNAIDS/WHO's ethics guidance points¹ or the IOM's recommendations¹⁵; 1 item was derived from the UNAIDS/AVAC's guidance documents for good participatory practices⁹⁷, and 11 items were informed by ethical concerns reported in other scientific/news media articles reviewed.

- 4) Finally, I fitted the 101 ethical items to the 8 principles and 31 ethical benchmarks proposed by Emanuel *et al.*'s (Appendix 5)⁹². I formulated each item under each benchmark as an affirmative one line-statement, so they would each represent a practical ethical consideration. Such adjustments to Emanuel *et al.*'s framework were in the spirit of its original formulation. Indeed, the authors mentioned that "[the principles] *must be elaborated by traditions of interpretation and require practical interpretation and specification. The benchmarks offer a first level of specification, indicating how to fulfill these principles. However, the details of this specification will inherently be context and culture dependent. This (...) simply recognized that applying ethical principles in the world requires taking facts into account, and these facts depend upon the context.*"⁵⁶ Hence, the 101 items represent a second level of specification, based on HIV PrEP literature, for my ethics appraisal.

At the end of this process, Principle 1 (collaborative partnership: 6 benchmarks) had 20 items; Principle 2 (social value: 4 benchmarks) had 7 items; Principle 3 (scientific validity: 3 benchmarks) had 33 items; Principle 4 (fair selection of study population: 3 benchmarks) had 6 items; Principle 5 (favourable risk-benefit ratio: 2 benchmarks) had 4 items; Principle 6 (independent review: 3 benchmarks) had 10 items; Principle 7 (informed consent: 5 benchmarks) had 12 items; and Principle 8 (respect for recruited participants and study community: 5 benchmarks) had 9 items. Clarifications and association to reference documents were added in endnotes to facilitate interpretation and harmonize appraisal by independent reviewers. For easier referencing, each principle, benchmark and item was numbered.

Quantitative ethics analysis.

I developed my own ethics checklist to facilitate my systematic ethics appraisal, for each study included. Essentially, a given item was checked if 1) the corresponding information was clearly identified in a source document (i.e., in trial registry file, in protocol, in consent form or in report) *and* 2) nothing within the same source document was deemed to contradict that information.

I made a series of calculations, in three steps, to determine **proportions of ethics items reported** for each study, by principle and overall. Those statistics were to serve as quantitative estimates of the extent to which ethical principles were fulfilled, based on my checklist. This facilitated comparisons across trials and across the 8 ethics principles. Summary statistics obtained were used to synthesize results.

First, I determined crude totals for each study appraised for ethics. Totals were such that studies reporting more ethics considerations from the checklist would obtain higher results:

STEP 1

Crude principle-total = total number of items checked, for each principle

Crude total = summation of the 8 crude principle-totals, for each study

Second, I calculated the percentage of items reported, at the principle level, for each study appraised for ethics. In order to prevent ascertainment bias, I ignored items that were clearly not appropriate for a particular study when appraising that study (e.g., items related to pregnancy in a study involving solely men who have sex with men). Whenever items were ignored for irrelevance, proportions were based on a different denominator (i.e., *maximal principle-total* inferior to 101, as shown below):

STEP 2

Crude principle-proportion = crude principle-total / maximal principle-total, for each principle

ETHICS SUB-SCORE = crude principle-proportion x 100%

Third, I standardized the proportions of items reported. This was to account for the fact that some principles had more checklist items than others (from 4 to 33 items per principle). Standardization is “a set of techniques used to remove as far as possible the effects of differences in age or other confounding variables when comparing two or more populations. (...) The directly standardized rate represents what the crude rate would have been in the study population if that population had the same distribution as the standard population with respect to the variable(s) for which the adjustment of standardization was carried out”²⁸. Here, standardization was to minimize the effect of differences in the number of items per principle. For the purpose of computation, I based my “standard” on the assumption that all eight ethical principles are equally important, that is, they each represent 12.5% of the standard total. In the spirit of Emanuel et al.’s framework, this is a conservative approach. Indeed, the authors stated that “[t]he presumption is that [these eight principles] must all be fulfilled for a research to be ethical” but also that “there is no simple algorithm for determining how to

balance or weigh these principles (...). Different researchers and communities will balance the principles in different ways (...)."⁵⁶ Standardized proportions (ethics scores) so obtained indicate the percentage of ethical considerations reported, "adjusted" for the number of checklist items per principle, for a given study:

STEP 3

Standardized principle-proportion = crude principle-proportion x 12.5%

ETHICS SCORE = summation of the 8 standardized principle-proportions

(From Aschengrau et al. 2007, pages 69-72)⁹⁸

For my ethics analysis, the statistics of interest were the **ethics scores** (adjusted proportion of checklist items reported, at study level) and the **ethics sub-scores** (adjusted proportion of checklist items reported, at principle level). I also determined the **number of study teams reporting each checklist item** (n), as well as the **number of studies appraised for which each item was relevant** (N).

Disaggregated data on items checked, for each study, were electronically captured in a customized *Microsoft Excel*[®] spreadsheet (Microsoft, Inc., version 2003). That spreadsheet was used to facilitate the calculation of the ethics scores and sub-scores, and to generate summary tables and figures.

DATA ITEMS FOR OBJECTIVE 4: DATA FROM PrEP TRIALS

Studies that had yielded data were identified, whether results had been published or not. Data obtained were reviewed and summarized by categories: 1) study designs and baseline characteristics of participants, 2) regimens tested, 3) safety, 4) efficacy, 5) adherence/compliance, 6) considerations for resistance, and 7) acceptability. Summarization occasionally required some calculations, based on reported data, in order to yield statistics of interest and/or to facilitate comparisons across studies.

5.8. QUALITY ASSESSMENT

Similarly to data extraction, quality assessment was based on the review of 4 categories of source documents: study reports, consent forms, study protocols, and trial registry files. And the same precedence rule as for data extraction was applied. In case of inconsistency across source documents, study report prevailed on consent form, which prevailed on protocol, which prevailed on registry file. In case of a missing source document, data items were to be searched in and extracted from the next document available, as per the precedence rule.

QUALITY OF REPORTING

For **trial registry files**, the time lag between the registration date and the reported start date was calculated for each study. For **protocols**, presentation features were summarized: date, version number, text length (using the *Microsoft Word® Readability* function, excluding header and footer content), number of other HIV oral PrEP trials cited, number of references listed, and mention of systematic reviews in reference list (based on reference titles).

A distinct form was developed to analyze the content of the **enrolment consent forms** ([Attachment 4](#)). It included 1) a section for identification, 2) a section for description, 3) a section for readability, and 4) a section for content. For the readability section, the consent form text was fully read, and statistics were generated using the *Microsoft Word® Readability* function - excluding header and footer content -. This tool was used to facilitate the determination of word counts (text length) and average words per sentence (syntactic complexity). Although Microsoft can also generate statistics on the reading level (e.g., Flesh Reading Ease, Flesch-Kincaid)⁹⁹, which are commonly used in scientific research¹⁰⁰, those statistics were not considered of interest for this review. This is because their formula and their interpretation are based on standards validated for average adults exposed to USA educational system. So, on top of inherent flaws¹⁰¹, those measures may not be valid to assess consent forms in international trials. Also, unfortunately, time and resources to complete my review were limited and I could not afford to do a systematic qualitative analysis of the language level (e.g., percentage of technical or “difficult” words). So, for the content section, I used *UNAIDS Guidance Point 16* as a standard. This Guidance Point discusses ethics considerations related to *Informed consent*. In that chapter, a few paragraphs list “*specific details*” that should be given to prospective study participants, “[i]n addition to the standard content of informed consent” (pages 53-54)¹. I singled out individual “details” so as to re-write those paragraphs in point-form. I obtained a list of 17 points ([Attachment 4](#), section 4).

For **study reports**, the quality of reporting was assessed using either the CONSORT statement (*CONsolidated Standards Of Reporting Trials*)¹⁰² or the TREND statement (*Transparent Reporting of Evaluations with Nonrandomized Designs*)¹⁰³, as relevant. The CONSORT statement is "an evidence-based tool to help researchers, editors and readers assess the quality of the reports of trials" (www.consort-statement.org/about-consort/). It is a validated tool that is composed of a list of 22 items "to include when reporting a randomized trial". The higher the total of items found in a study report, the better its reporting quality. The TREND statement is a checklist proposed for the assessment of the reporting quality of non-randomized trials (www.trend-statement.org). It is composed of a list of 46 "bullet points" organized in 22 items. The higher the total of items found in a study report, the better its reporting quality. No evidence of validation was retrieved for this tool. However, it is listed on the *Equator Network* website (www.equator-network.org), "an international initiative that seeks to improve reliability of medical research literature by promoting transparent and accurate reporting of research studies".

STANDARD QUALITY ASSESSMENT

I also assessed the methodological quality of the HIV PrEP studies using two standard instruments, as such tools are available and commonly used in appraising clinical studies.

The *Jadad* 5 point-scale¹⁰⁴ is validated for the quality assessment of clinical trials, based on study *reports*. It has 3 domains: randomization (2 points), blinding (2 points) and withdrawals (1 point). The maximal score is 5, with a higher score corresponding to higher quality, and scores of 3-5 considered as good quality. For practical purposes, I slightly modified this scale so I could use it with other study documents (e.g., based on analytic plan), as I expected that most studies would have no report available ([Appendix 6](#)). This can be justified since, in principle, statistical methods exposed in a protocol should be the similar in the report of the study. Plus the tool developers suggested the potential use of the scale with protocols¹⁰⁴.

The *Newcastle-Ottawa Quality Assessment Scale* (NOS)¹⁰⁵ was developed to assess the quality of *non randomized* studies in systematic reviews; it has distinct scales for case-control studies and for cohort studies. The scale for case-control studies has 3 domains: selection (4 stars), comparability (2 stars) and exposure (3 stars). The scale for cohort studies has 3 domains: selection (4 stars), comparability (2 stars) and outcome (3 stars). For both scales, the maximal score is 9 stars, with a higher score corresponding to higher quality.

RISK OF BIAS ASSESSMENT

The risk of bias in individual studies was appraised using the Cochrane Collaboration's *Tool for Assessing Risk of Bias*, in systematic reviews^{106, 107}. This tool presents a list of 6 questions about potential risk of bias related to 1) allocation sequence generation; 2) allocation concealment; 3) blinding of participants, personnel and outcome assessors; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other sources of bias. **At the study level**, I answered each question by "yes", "no" or "unclear", as per the tool's guidance. Questions that could not be answered (typically, in the absence of a report) were considered "not applicable", although this option is not listed in the original tool, as it is to be used with study reports. Other sources of potential selection bias and of ascertainment bias were identified and similarly appraised, for each study included. **At the outcome level**, I judged the level of bias in the assessment of safety and of efficacy/effectiveness as "low", "high" or "unclear", as perceived, both within and across included studies.

5.9. ADDITIONAL ANALYSES

SUB-GROUP ANALYSES

I conducted sub-group analyses of study quality (Jadad scores) and ethical considerations (ethics scores and sub-scores) to assess the influence of the completeness of source document sets, the regions hosting the trials, the studies' primary question, and the status of studies. I chose these factors because I thought, *a priori*, that they might modify the amount of data items reported.

CORRELATION ETHICS CONSIDERATIONS – STUDY QUALITY

Ascending ethics scores and sub-scores were plotted against corresponding Jadad scores, to graphically assess the correlation between ethics considerations and study quality. I chose to do this because I was interested in seeing if high study quality - as measured by a common validated tool - would correspond to a better reporting of ethics considerations.

EXPLORING HETEROGENEITY

Outliers were identified in the primary ethics analysis as studies with particularly low ethics scores. They were removed from the dataset, and their influence was explored through further sub-group ethics analyses.

5.10. SYNTHESIS OF RESULTS

SUMMARY FOR OBJECTIVE 1: IDENTIFICATION OF PrEP TRIALS

A summary figure was designed to present the chronology, lead principal investigator, sample size, study population, phase, test-drug, host country(ies), and status of identified HIV oral PrEP trials.

SUMMARY FOR OBJECTIVE 2: METHODS IN PrEP TRIALS

The most common design in HIV oral PrEP was identified. The percentage of studies with a Jadad score of 3 or more was determined. Jadad scores were chronologically arranged, on a graph, based on source documents dates. A trend line was generated (in Excel®) to illustrate the time trend for the quality of PrEP studies. The overall risk of bias was reported, at the outcome level.

SUMMARY FOR OBJECTIVE 3: ETHICS APPRAISAL OF PrEP TRIALS

I identified checklist items reported by none of the teams and those reported by all teams. I compared ethics scores and ethics sub-scores; and I calculated their medians across studies and across ethics principles. Ethics principles for which ethics considerations tended to be least /most addressed were identified, based on median sub-scores calculated across studies. For each principle, ethics sub-scores of studies appraised were chronologically arranged, on a graph, based on source documents dates. A trend line was generated (in Excel®) to illustrate the time trend for the reporting quality of ethics considerations in PrEP studies.

SUMMARY FOR OBJECTIVE 4: DATA FROM PrEP TRIALS

Should a meta-analysis have been feasible and relevant, I was to pool estimates of efficacy and safety of HIV oral PrEP. Otherwise, I had planned to summarize available evidence on PrEP efficacy and safety.

5.11. AMENDMENTS TO ORIGINAL PROTOCOL

I relaxed two inclusion criteria from my original protocol. The **HIV transmission mode**, initially restricted to sexual transmission was expanded to include blood-borne transmission route. And the **primary outcome** measures, initially restricted to efficacy and safety measures, were expanded to any kind of measure, as long as outcome measures included at least one measure of efficacy or of safety. This was to be more inclusive, considering that HIV oral PrEP trials share similar ethical challenges. And the additional number of eligible studies did not affect the feasibility of my thesis.

The US National Institutes of Health trial registry was searched using **trials categories** (e.g., interventional studies) rather than keywords, as that option was available and improved the sensitivity of the search strategy. **No journal was hand-searched** for eligible study reports, as initially planned, because I felt that it would not yield further findings. **Most sponsors were not contacted**, as investigators - approached first, except in one case - have the authority to release study documents. Finally, **it was deemed unnecessary to query investigators to confirm the completeness of the list of HIV oral PrEP studies**: attendance to major HIV/AIDS conferences and screening of communications presented in public meetings was sufficient to gather updates on PrEP research.

6.0 RESULTS

6.1. STUDY SELECTION

Search outputs identified a total of 5,074 records: 2,881 from registries, 55 from the World Wide Web, and 2,138 from electronic databases. Eight hundred and fifteen duplicates (within information source types) were removed. From the 4,259 records left for screening, 4,224 were excluded: 5 “topical PrEP” studies (HIV antiretroviral-based microbicides); 226 studies exploring prevention of mother-to-child HIV transmission with antiretrovirals; 244 non-PrEP biomedical HIV prevention interventions on seronegative persons; 20 non-PrEP biomedical HIV prevention interventions on seropositive persons; 15 HIV post-exposure prophylaxis studies; and 3,714 irrelevant studies (no focus on HIV, non interventional HIV-related studies, non prevention HIV-related interventions, non biomedical HIV prevention interventions). Thirty-five full-text documents were reviewed and 16 studies were included in the qualitative analysis, after 19 duplicates (across information source types) were identified. One study, although focusing on *topical* PrEP, was included because it features oral HIV oral PrEP as a comparator. Study selection flow diagram is presented in [Figure 1](#). The list of included studies is presented in [Table 1](#).

6.2. DATA COLLECTION PROCESS

Thirteen of the 16 selected studies were found in a registry¹⁰⁸⁻¹²⁰, 12 approved protocols and consent forms were collected (8 from investigators, 3 from specialized websites, 1 from a sponsor), and 3 study reports were retrieved¹²¹⁻¹²³. Only a study summary could be obtained for one of the registered studies¹²⁴, as no protocol had ever been *approved*. Although limited in length, that summary was used in lieu of the non-existent approved protocol. A full set of target source documents (registry file, approved protocol, consent form, report) could be obtained for only two studies; 3 of the 4 target source documents (registry file, approved protocol, consent form) could be obtained for nine studies; 2 of the 4 target source documents (approved protocol, consent form) could be obtained for one study; and 1 of the 4 target source documents (registry file or report) could be obtained for three studies. None of the 4 target source documents could be found for one study. That study was identified solely based on information available on the World Wide Web^{125, 126}. Those online source documents cover valuable but limited descriptive information, which did not allow for a full analysis. Reasons for not obtaining protocols/consent forms were that: investigator could not be reached before I completed my synthesis; protocol had never/not yet been approved; or contact person declined to release them.

6.3. DATA ANALYSIS

Because some HIV oral PrEP studies identified did not have sufficient documentation available, not all could be included in all analyses (Figure 1):

- **16 studies were considered under Objective 1: identification of PrEP trials**
- **15 studies were considered under Objective 2: methods in PrEP trials**
(1 study was left out because none of the target source documents was available)
- **14 studies were considered under Objective 3: ethics appraisal of PrEP trials**
(1 more study was left out due to its focus on topical PrEP, with oral PrEP used only as single dose control)
- **3 studies were considered under Objective 4: data from PrEP trials**
(only three studies have produced data)

DATA ANALYSIS FOR OBJECTIVE 1: IDENTIFICATION OF PrEP TRIALS (16 STUDIES)

How many HIV oral PrEP trials have there been?

Sixteen HIV oral PrEP clinical projects were identified. All have been initiated after the year 2000. Between 2003 and 2008, there have been between 2 and 6 active trials each year. And about 10 trials were active in 2009. For simplicity and for acknowledgement of intellectual property, individual trials will be referred to by the name of the lead investigator, throughout this manuscript. The list of lead investigators is as follows:

Jackson¹²¹, Peterson^{110, 123, 127, 128}, Page-Shafer^{108, 122, 129-131}, Grohskopf^{111, 132, 133}, Choopanya^{114, 134}, Hoffman^{109, 124}, Smith^{115, 135}, Thigpen^{116, 136}, Grant^{117, 137, 138, 138}, Celum^{112, 139}, Hendrix^{113, 140}, Van Damme^{118, 141, 142}, Chirenje^{119, 143}, Grosskurth^{87, 120}, Anton¹⁴⁴, and Hosek^{125, 126} ([Table 1](#)).

What is the status of the HIV oral PrEP trials?

Two studies were completed: Jackson¹²¹ and Peterson¹²³. Three studies were terminated early: Page-Shafer¹⁰⁸, Hoffman¹⁰⁹, Smith¹¹⁵. At the time I was completing my synthesis: 6 studies were ongoing (Grohskopf¹¹¹, Choopanya¹¹⁴, Thigpen¹¹⁶, Grant¹¹⁷, Celum¹¹², Hendrix¹¹³); 2 studies were active but not yet recruiting (Van Damme¹¹⁸ and Chirenje¹¹⁹); and 3 studies were in planning (Grosskurth¹²⁰, Anton¹⁴⁴, and Hosek¹²⁵). Grosskurth's study, also identified as IAVI-E002 (72 participants, in Uganda) was reportedly coupled with another study, IAVI-E001, for a total of 150 participants, including participants in Uganda⁸⁷. No further information was found about the IAVI-E001 study, at the time I completed my synthesis, but I considered it as a part of Grosskurth's study, in this review. The list of the 16 HIV oral PrEP trials is presented in [Table 1](#). Reported reasons for early closures are summarized in [Table 2](#).

Where have the HIV oral PrEP trials been conducted?

HIV oral PrEP trials have been planned and/or conducted in a total of 17 countries world-wide, with 10 studies involving sub-Saharan African host communities. Among the countries involved, 11 are in sub-Saharan Africa (Botswana, Cameroon, Ghana, Kenya, Malawi, Nigeria, South Africa, Tanzania, Uganda, Zambia, Zimbabwe), 3 in Latin America (Brazil, Ecuador, Peru), 2 in South-Eastern Asia (Cambodia, Thailand), and one in Northern America (United States of America) ([Table 3](#), [Figure 2](#)).

What populations have been considered for HIV oral PrEP trials?

Five distinct target populations have been considered for HIV oral PrEP trials: serodiscordant heterosexual couples (i.e., one partner HIV infected and one partner HIV seronegative: 2 trials), heterosexual men (6 trials), heterosexual women (10 trials), injecting drug users - or partners thereof (2 trials) -, and men having sex with men (4 trials). No specification was found about participants' sexual orientation in one study¹³⁴; for this review, they were assumed to be heterosexuals, although some participants might be homosexual or bisexuals. Three studies purposefully included seronegative persons who had seropositive partners, without focusing on such participants^{121, 135, 136}. One protocol team mentioned including homosexual women¹⁴⁴ ([Table 4](#)).

Across the 16 studies, the minimal age for eligibility is 18 years old or the local legal age for consent, and the maximal age is 65. The narrowest age range of eligible participants was 4 years and the widest was 47 years. Eligibility criteria also included adequate hepatic and renal function (15 studies), adequate bone health (7 studies), and adequate pancreatic function (5 studies). Hepatitis B was mentioned as an exclusion criterion in 12 out of 15 analyzed studies; 3 of those 12 study teams also had hepatitis C as an exclusion criterion. Eleven of the twelve studies including women had pregnancy and/or breastfeeding as an exclusion criterion.

All studies had at least one "HIV exposure" component(s) among their inclusion criteria. These have been based on the rate of sexual acts (6 trials), the rate of sexual partners (8 trials), unprotected sexual activity (3 trials), sexual partnership characteristics (3 trials), the exchange of sexual acts for material profit (2 trials), the use of injection drugs (2 trials), and/or a recent history of sexually transmitted infection (1 trial) ([Table 5](#)). One study has been focusing specifically on the prevention of blood-borne HIV infection (injecting drug users)¹¹⁴. The other 15 studies focused/focus on prevention of HIV sexual transmission (vaginal and/or rectal). Seven of those studies set substance abuse or injection drug use as an exclusion criterion.

What designs have been used in HIV oral PrEP trials?

Fifteen of the sixteen studies identified were designed as parallel randomized trials; one of those has multiple sequences, that is, groups are to take two different test-drugs, sequentially ¹⁴⁴. One study is a randomized crossover trial¹⁴⁰, and one was a non randomized controlled cohort study¹²¹. Nine trials feature 2 study groups; three trials feature 3 groups^{121, 126, 139}, two feature 4 groups^{132, 144}, one features 5 groups¹⁴³, and one features 6 groups¹⁴⁰. Sample sizes range from 18 to 4,200 participants, with a mean of 1,461 participants per trial, and a total of 20,451 participants to be involved - excluding 1,360 who were never enrolled -^{109, 122} ([Table 4](#)).

The primary questions reported in HIV oral PrEP trials include safety or extended safety (15 trials), efficacy or effectiveness (9 trials), tolerability (3 trials), adherence (3 trials), acceptability (3 trials), pharmacological

outcomes (3 trials), feasibility (2 trials), and behavioural outcomes (1 trial). Studies are presented as being: for “preparedness” (1 trial); phase I (1 trial); phase I/II (2 trials); phase II (3 trials); phase II/III, 2a or 2b (5 trials); or phase III (4 trials). One study focused on *topical* pre-exposure prophylaxis, although featuring oral tenofovir as a comparator¹⁴⁴ (Table 6).

What antiretrovirals have been tested in HIV oral PrEP trials?

Ten studies were designed to test tenofovir (TDF, Viread®), seven to test emtricitabine/tenofovir (FTC/TDF, Truvada®), and one to test nevirapine (NVP, Viramune®). Two studies are to test both tenofovir and emtricitabine/tenofovir pills. Comparators include matched placebo pills (13 trials), tenofovir topical gel (vaginally applied: 2 trials, rectally applied: 1 trial), “self-control” (1 cross-over randomized trial, 1 multiple-sequence randomized trial), other antiretroviral pill (2 trials), escalated doses of test-drug (1 trial), delayed identical regimen/placebo (1 trial), intermittent regimen (1 trial), and no pills (1 trial) (Table 4).

Who has been leading and supporting HIV oral PrEP trials?

All 16 HIV oral PrEP projects have been led or co-led by one or more scientist(s) affiliated to institutions based in the United States of America. USA-based lead investigators are affiliated to the following institutions: Centers for Disease Control and Prevention (Atlanta, Georgia: 4 studies), University of California in San Francisco (San Francisco, California: 3 studies), Family Health International (Research Triangle Park, North Carolina: 2 studies), Johns Hopkins University (Baltimore, Maryland: 2 studies), University of Washington (Seattle, Washington: 2 studies), John H. Stroger Jr. Hospital of Cook County (Chicago, Illinois: 1 study), University of California in Los Angeles (Los Angeles, California: 1 study), University of North Carolina at Chapel Hill (Chapel Hill, North Carolina: 1 study). Eight protocol teams named, among their collaborators, between 1 and 6 investigators involved in other HIV oral PrEP trials.

Six HIV oral PrEP projects had/have co-lead investigators based outside of the USA. One project was co-chaired by an Australia-based investigator (University of New South Wales) and co-led by a Cambodia-based protocol collaborator (National Center for HIV/AIDS, Dermatology, and STDs/Ministry of Health of Cambodia)¹²⁹. One study is co-chaired by a Peru-based investigator (*Investigaciones Médicas en Salud*)¹³⁷. Two trials had/have co-investigators affiliated to a USA-Botswana collaborative project (BOTUSA)^{135, 136}. One trial was co-chaired by an investigator affiliated to a USA-Zimbabwe collaborative project (UZ-UCSF Collaborative Research Programme)¹⁴³. One study is led by two Uganda-based investigators (MRC Entebbe), with a USA-based investigator cited as the “Responsible Party”¹²⁰.

Nine main sources of material support (financial or in-kind) were identified, all based in the USA: 3 governmental organizations, 2 non-governmental organizations, 1 academic institution, 1 academic-governmental partnership, 1 public-private partnership, and 1 pharmaceutical company. Governmental organizations are: the *Centers for Disease Control and Prevention* (involved in 4 trials), the *National Institutes of Health* - or one of its programs or offices - (8 trials), and *United States Aid for International Development* (1 trial). Non-governmental organizations are: the *Bill and Melinda Gates Foundation* (5 trials) and *Family Health International* (4 trials). The *University of Washington* is sponsoring 1 trial. "CONRAD was established (...) under a cooperative agreement between Eastern Virginia Medical School (...) and the U. S. Agency for International Development (...)" (www.conrad.org) and is involved in 3 trials. The *International AIDS Vaccine Initiative* is supporting 1 trial; the members of its Board of Directors "bring a wide range of expertise and experience to IAVI from government and industry and from private foundations and non-governmental organizations" (www.iavi.org). And *Gilead Sciences, Inc.*, a pharmaceutical company, is involved in 13 trials (Table 7).

DATA ANALYSIS FOR OBJECTIVE 2: METHODS IN PrEP TRIALS (15 STUDIES)

Participants' recruitment methods

Information about recruitment methods was found for 13 studies of the 15 studies analyzed; the other 2 studies had either no protocol or no report available. Participants were reportedly recruited using a combination of methods: through a healthcare institution (9 studies), through a public campaign (8 studies), through a community-based organization (8 studies), through a designated recruiting agent/agency (6 studies), and/or through referrals (7 studies). Five study teams were to recruit through other local study teams or study registry of volunteers, and the two teams targeting female sex workers mentioned "*places of employment*" or "*high HIV transmission areas*".

Tested antiretroviral regimens

For 14 of the 15 studies analyzed, antiretroviral pills have been used at therapeutical doses for tenofovir (300mg daily) and emtricitabine/tenofovir (200mg/300mg daily). One study used a set of infra-therapeutical doses of nevirapine (200 to 800mg weekly). Fourteen regimens tested are continuous (i.e., pre-determined intake schedule) whereas one included an intermittent regimen in its design. Tested oral interventions have been prescribed for a single dose to 48 months of continuous daily dose (with some flexibility) ([Table 8](#)).

Co-interventions

Some interventions were to be given systematically to all participants, regardless of their group of assignment. Those co-interventions included HIV behavioural risk-reduction counselling for 14 studies. Co-interventions also included: provision of unspecified condoms (4 studies), provision of male condoms (4 studies), and provision of both male and female condoms (4 studies). Five of the twelve study teams that were to provide condoms were also to provide related directions for proper use thereof. Four study teams were to provide HIV testing for participants' sexual partners and one was to make couple's counselling available. Treatment of sexually transmitted infections was to be offered by five study teams. Four study teams were to offer hepatitis B vaccination series. One study will require participants to abstain from vaginal and anal sex during the active phases of the follow-up period. One study team (focusing on injecting drug users) was to provide methadone, as well as bleach and instructions to use bleach for cleaning injection equipment.

One team mentioned the willingness “to undergo couple HIV testing, sexually transmitted infection (STI) screening, HIV counselling and receive test results, and share results with partner” as an inclusion criterion. It was unclear whether the counselling referred to HIV pre- and post-test or to risk-reduction, and whether those criteria encompassed couple's counselling.

Outcome measures

All but one of the 15 studies analyzed featured at least 2 *primary* questions, which included safety or extended safety, efficacy or effectiveness, tolerability, adherence, acceptability, pharmacokinetics outcomes, feasibility, and behavioural outcomes (Table 6).

Safety

In the 15 studies analyzed, outcome measures listed to monitor **physical/physiological safety** have included: measures of renal function (15 studies), measures of hepatic function (14 studies), measures of bone health (12 studies), and reported adverse events (15 studies). Four study teams reported monitoring hepatitis B serostatus. And two study teams reported monitoring hepatitis C serostatus; those teams were not among the three that had hepatitis C as an exclusion criterion. Five study teams reported monitoring for sexually transmitted diseases. All study teams but two reported the use of at least one grading system for the assessment of adverse events (e.g., the USA National Institutes of Health's Division of AIDS's *Table for Grading Adult and Pediatric Adverse Events*).

All 15 studies analyzed mentioned some assessment of “**behavioural safety**”. Most outcome measures were self-reported, and relate to: rate of partners/new partners (8 studies), use/non use of condoms during sex (11 studies), rate of sexual acts (7 studies), sexual partners' characteristics (3 studies), and frequency of injection drug use/needle sharing (1 study). Behavioural outcomes were not always clearly defined (e.g., “*high risk activity*”, “*change in behaviour*”). They were frequently not found within the list of outcomes, but somewhere else in the text, or only in tables. Although not consistently reported across studies, methods to assess risk-taking behaviours included quantitative, qualitative or mixed instruments such as questionnaires, structured or in-depth interviews, and Audio Computer-Assisted Self-Interview (ACASI). Two study teams mentioned the rate of diagnosed sexually transmitted infections (throughout the follow-up period) as an *objective* measure of behavioural safety.

Out of the 15 studies analyzed, nine teams mentioned some assessment of “**social safety**”. Self-reported adverse events deemed expectable included issues related to breach of privacy/confidentiality (8 studies), coercion/stigmatization (6 studies), negative interferences with gainful employment (5 studies),

distressful/harmful social interactions (3 studies), relational difficulties (3 studies), and unfair treatment (3 studies). Like behavioural outcomes, social harm outcomes were not always clearly defined (e.g., “*social harms that are judged by the [Investigator of Record]/designee to be serious or unexpected*”). They were frequently not found within the list of outcomes, but somewhere else in the text. However, some protocol teams had a distinct section for social harms or classified those as “*social adverse events*”. One study team, although reporting the availability of a *Social Risk Events Form*, stated that no such events were expected in the trial.

Other safety outcome measures mentioned as such included: adverse events in participants' sexual partners (3 studies) and substance abuse (1 study).

Efficacy/effectiveness

In the 15 studies analyzed, the main reported outcome measure for efficacy/effectiveness was the rate of HIV seroconversions (11 studies). Four study teams reported assessment of delayed HIV seroconversions (i.e., positive HIV antibody testing a certain time after intake of last dose of product).

Seroconversion-related outcomes

Out of 15 studies analyzed, ten study teams reported specific outcome measures for the assessment of seroconverters' immune system: HIV viral load / viral setpoint and count of CD4 lymphocytes T. Among those teams, all were to test blood samples, and one was to also test male and female genital secretions samples. All ten study teams (9 efficacy/effectiveness trials, 1 safety trial) mentioned they would perform resistance testing of breakthrough viruses.

Adherence

Objective outcome measures for the assessment of adherence were found for all 15 studies analyzed. They included: count of unused returned pills (12 studies) and systematic or periodic directly observed treatment (5 studies). Two study teams mentioned automatic drug use data collection, using MEMS® caps; MEMS® is an electronic medication event monitoring system allowing collection of data such as the number of times the bottle was opened, and the dates and the times at which it was opened¹⁴⁵. Fourteen study teams reported measurement of test-drug blood / intracellular levels or pharmacokinetics measurements (e.g., area under the curve, C_{max} , C_{min}). But only 7 of those 14 teams listed such measurements as *adherence measures*.

Subjective outcome measures for adherence were considered by 12 study teams, and all relate to self-reported product use/non use: number/proportion of doses taken, number/proportion of doses missed, proportion of participants taking a certain proportion of pills provided, and/or timing of daily drug intake. Methods to collect those data were not consistently found but they included: not otherwise characterized interviews/structured questionnaires (7 studies), diary reports (5 studies), computer-assisted self interview (5

studies), and/or interviewer-administered questionnaire (4 studies). Study procedures included systematic adherence counselling (10 studies), and measures of contamination secondary to drug selling to / drug sharing with enrolled seropositive sexual partner or participants in the control arm (11 studies).

Other outcomes

Other outcomes measured in the 15 HIV oral PrEP trials analyzed included: pharmacological measures (12 studies: *not* for adherence) and feasibility/acceptability (7 studies).

Test-drug discontinuation criteria

In the 15 studies analyzed, investigator-initiated drug discontinuation criteria included laboratory abnormalities and/or clinical adverse events (13 studies), HIV seroconversion (12 studies), intercurrent pregnancy/breastfeeding (10 studies, out of 12 enrolling women), intake of prohibited concomitant medications (6 studies), compliance issues (5 studies), hepatitis B seroconversion (3 studies), and imprisonment (1 study). Discontinuation was consistently permanent, across studies, for HIV seroconversion and hepatitis B seroconversion.

Follow up duration

For the 15 studies analyzed, tested interventions were prescribed for a duration ranging from about 9 days to 48 months, with 10 study teams mentioning some flexibility in the follow-up duration. Twelve study teams made plans to have a period of follow-up after the last dose given: off-drug follow-up was between 1 week and 8 weeks. Off-drug follow-ups intended to assess hepatitis B rebound after drug cessation, delayed adverse events, evolution of adverse events, or delayed HIV seroconversions (due to plausible fading protective effect, or due to potentially suppressed HIV infection during therapy). Off-product follow-up period could be extended for HIV antibody seroconverters, hepatitis B surface antigen seroconverters, or for female participants who became pregnant. One study had a 9 month off-product follow-up period for half their participants, but *before* initiation of test-drug regimen ("delayed" tenofovir or "delayed" placebo: [Table 4](#); [Table 8](#)).

Medical care during follow-up

Out of 15 studies analyzed, 5 namely identified the healthcare institution(s) where ill participants would be referred to for further care, during the follow-up period - although some mentioned that study staff might initiate treatments -. However, 13 teams presented a more or less detailed care plan for the management of adverse events in study participants. Care plans for adverse events were typically based on their gravity, relatedness to study drug, evolution and number of occurrences. Two study teams clearly stated that there would be *no* monetary compensation for harm caused by study drug intake whereas five study teams did mention a compensation plan for study-related harm ([Table 8](#)).

HIV detection strategies

The HIV type to be tested in laboratory was consistently specified across the 15 studies analyzed, typically under the section on main objectives/endpoints or in HIV detection algorithms: type 1 (12 studies) or both types 1 and 2 (3 studies). Fourteen study teams presented an algorithm for the diagnosis of HIV infection, either only within the text of a source document (4 trials), or both within the text and as a figure (10 trials). Overall, 24 strategies were presented (up to 3 strategies per trial). Six of the fourteen teams presented a single algorithm, six teams presented 2 distinct algorithms, and two teams presented 3 distinct algorithms. When they were to be used at different study stages, multiple strategies included distinct algorithms: for screening, screening/enrolment, enrolment/follow-up, follow-up, or unscheduled visit. When they were to be used based on participants' characteristics, multiple strategies included distinct algorithms: for all participants, for persons participating concomitantly in a local HIV vaccine trial, or for participants in which acute infection would be suspected.

Most study teams reported HIV prevalence in host community, either at a regional level (e.g., Sub-Saharan Africa: 3 trials), or at the country level (1 study) or at the city/community level (4 studies). One study team reported using a testing algorithm that was conform to the host country's national government regulations, and two teams reported previous validation of their HIV detection algorithm in the context of host community. HIV testing approaches presented were: serial (7), parallel (6), mixed serial/parallel (6), neither serial nor parallel (3 single-test strategies), or unclear (2). Monitoring of HIV serostatus was to be done 4 weeks after last product dose (1 study with a follow-up period of 12 weeks), upon first and last visits (1 study with a follow-up period of 13 weeks), weekly (1 study with a follow-up period of 21 weeks), monthly (9 studies), or every 3 months (1 study). Information about HIV testing frequency was not found for 2 studies.

HIV antibody detection was to be ascertained by at least one of the following: rapid HIV test (12 trials),

enzyme-linked immunosorbent assay (ELISA: 10 trials), Western Blot (WB: 9 trials), or immunofluorescence assay (IFA: 1 trial). One algorithm included combined antibody/antigen detection using *Genscreen*^{® 146}(1 trial). Seven teams - all focusing on efficacy/effectiveness - planned to assess the timing of infection *before* detectable antibody seroconversions, before initiation of the PrEP intervention and/or *after* the last PrEP dose ([Table 9](#)).

Considerations for pregnancy

Twelve of the 15 studies analyzed included women: 5 with women only, 5 with both men and women, 2 with serodiscordant couples ([Table 4](#)). Eleven of those twelve studies had pregnancy and/or breastfeeding as an exclusion criterion. Overall, nine of the twelve trials including women had specifications regarding non-condom contraceptives, non-condom contraceptive services and/or referrals to non-condom contraceptive products/services, during follow-up. Non-condom contraception could be either *not* required as an eligibility criterion and *not* provided as a co-intervention (2 studies), or required as an eligibility criterion *but not* provided as a co-intervention (1 study), or *not* required as an eligibility criterion *but* provided as an optional co-intervention (1 study), or both required as an eligibility criterion *and* provided as a co-intervention (8 studies). Two of the three study teams that were not to provide non-condom contraceptives reported providing condoms.

Ten study teams reported intercurrent pregnancy/breastfeeding as a criterion to discontinue test-drug; four offered the option to resume test-drug after end of pregnancy and breastfeeding period. Eight study teams reported some strategy to explore test-drug(s) safety for pregnant women and their foetuses (*checklist item 5.1.2*); those 8 teams also planned some level of follow-up of pregnant women for safety (*checklist item 5.1.3*). Two study teams reported a comprehensive care plan for participants becoming pregnant (*checklist item 3.2.26*) as recommended by the *Institute of Medicine*¹⁵ ([Attachment 3](#) and [Table 10](#)).

Statistical considerations

Fourteen of the 15 studies analyzed provided some information to justify their sample size. Twelve of those fourteen studies reported some estimate of cumulative expected withdrawals, which varied between “very low” to 20%. Eight of those study teams did not justify their withdrawal estimates, five based their estimates on scientific data *not* from similar target population and/or similar intervention, and two based their estimates on data from a similar target population and/or from a similar intervention.

Twelve study teams mentioned interim analyses to be performed during the follow-up period. Eight study teams intended to use a stopping rule for their study: 5 had a rule for harm, 5 had a rule for futility, and 6 had a rule for benefit. Four of the 8 teams mentioned all three rules. All but one of those 8 teams were/are focusing on efficacy/effectiveness.

Efficacy/effectiveness studies

Nine of the 15 trials analyzed had efficacy or effectiveness as a primary outcome (Table 6). All corresponding study teams reported an estimate of the test-drug(s) efficacy, i.e., the expected capacity of the drug to reduce the likelihood of seroconversion, which they used for sample size calculation. For the trials testing the efficacy/effectiveness of tenofovir, the estimated “true efficacy” varied between 55 and 83% of reduced seroconversions, whereas the efficacy to be observed, used for the null hypothesis, varied between 10 and 50%. For the trials testing the efficacy/effectiveness of emtricitabine/tenofovir, the estimated “true efficacy” varied between 55 and 70%, whereas the efficacy to be observed, used in for the null hypothesis, varied between 10 and 30%. Five of the nine study teams focusing on efficacy/effectiveness based their estimates of product efficacy on assumptions, two based their estimates on scientific data *not* from similar population and/or similar intervention, and two based their estimates on data from a similar population and/or from a similar intervention.

All 9 study teams focusing on efficacy or effectiveness reported an estimate of the expected HIV seroconversion rate during the trial. That estimate varied between 2.0 and 9.0 per 100 person-years, but only two teams had estimates above 5%. Five study teams used a combination of data sources, for the estimation of HIV seroconversion incidence during follow-up (Table 10, checklist item 3.2.2).

All 9 study teams focusing on efficacy/effectiveness planned to use an intent-to-treat approach for the analyses of data collected; three teams also used a per-protocol protocol approach; and three teams also used another approach (modified/adjusted intent-to-treat).

DATA ANALYSIS FOR OBJECTIVE 3: ETHICS APPRAISAL OF PrEP TRIALS (14 STUDIES)

Fourteen of the 16 studies included in the review were ethically appraised. Hosek's study was excluded because none of the targeted source documents were available^{125, 126}. Anton's study was excluded because it focuses on *topical* pre-exposure prophylaxis (ineligible intervention for this review), although featuring oral PrEP as a single dose comparator¹⁴⁴. The number of studies for which each checklist item was identified for each principle is presented in [Table 10](#).

Ethics considerations reporting, at the study level (average proportions of ethics considerations reported, across principles: [Figure 3](#))

The ethics scores varied between 6 and 76%, with a median of 56% and an IQR=[39-64] %, across principles. Among the 14 studies appraised for ethics, three outliers were identified as having the 3 lowest scores (6, 6 and 21%).

Ethics considerations reporting, at the principle level (average proportions of checklist items reported, across studies: [Figure 3](#), [Figure 4](#))

The ethics sub-scores are reported below, principle by principle.

Principle 1: collaborative partnership

Ethics sub-scores for this principle ranged from 0 to 65%, with a median of 48% and an IQR=[21-50] %. No item for this principle was consistently identified in all studies. One item (1.1.1) was consistently missing in all studies; that item reads as follows:

“strategy to ensure legitimacy of community partners chosen to represent host community”.

Principle 2: social value

Ethics sub-scores for this principle ranged from 0 to 86%, with a median of 31% and an IQR=[20-57] %. No item for this principle was consistently identified in all studies. No item was consistently missing in all studies.

Principle 3: scientific validity

Ethics sub-scores for this principle ranged from 13 to 79%, with a median of 55% and an IQR=[36-63] %. One item for this principle (3.2.13) was consistently identified in all of the studies; this item reads as follows:

"description of monitoring plan for adherence".

Three items (3.2.7, 3.2.8, 3.2.10) were identified in none of the studies; those items read as follows:

"use of both blinded and unblinded control group"

"randomized comparisons of behavioural risk-reduction interventions incorporated into design"

"behavioural co-intervention was field tested during planning phase"

Principle 4: fair selection of study population

Ethics sub-scores for this principle ranged from 0 to 100%, with a median of 67% and an IQR=[21-83] %. No item for this principle was consistently identified in all studies. No item was consistently missing in all studies.

Principle 5: favorable risk-benefit ratio

Ethics sub-scores for this principle ranged from 0 to 100%, with a median of 63% and an IQR=[31-75] %. No item for this principle was consistently identified in all studies. No item was consistently missing in all studies.

Principle 6: independent review

Ethics sub-scores for this principle ranged from 20 to 70%, with a median of 50% and an IQR=[40-60] %. One item for this principle (6.2.2) was consistently identified in all studies; this item reads as follows:

"funding source(s)/ in-kind support disclosed".

Two items (6.3.1, 6.3.2) were consistently missing in all studies; these items read as follows:

"specification of measures taken to ensure independence and competence of ethics review"

"specification of measures taken to prevent situations of conflict(s) of interest".

Principle 7: informed consent

Ethics sub-scores for this principle ranged from 0 to 92%, with a median of 58% and an IQR=[47-83] %. No item for this principle was consistently identified in all studies. No item was consistently missing in all studies.

Principle 8: respect for recruited participants and study community

Ethics sub-scores for this principle ranged from 0 to 78%, with a median of 56% and an IQR=[47-56] %. No item for this principle was consistently identified in all studies. No item was consistently missing in all studies.

Trends in ethics considerations reporting

Principle 4: fair selection of study population had the highest median ethics sub-score (67 %) and *Principle 2: social value* had the lowest median ethics sub-score (31 %), across trials ([Figure 3](#)). There was some degree of dispersion in sub-scores, within each principle. *Principle 8: respect for recruited participants and study community* showed the least variation (IQR=[47-56] %), while *Principle 4: fair selection of study population* showed the most variation (IQR=[21-83] %), across studies. When studies were chronologically ordered (from the earliest to the most recent set of source documents reviewed), all principles showed a positive time trend in their ethics sub-scores (based on linear regression). Of note, though, the earliest two studies and the most recent study in the timeline had no approved protocol or consent form available for appraisal. ([Figure 4](#)).

Reported ethics guidance documents

Twelve of the fourteen study teams mentioned ethics guidance documents of reference. Among those, 11 study teams mentioned international ethics guidelines (*Declaration of Helsinki* or *International Conference on Harmonisation-Guidelines for Good Clinical Practice*), in addition to guidelines developed in the sponsoring country (e.g., USA Code of Federal Regulations, USA Food and Drug Administration). One of the 12 study teams mentioned only ethics guidelines developed in the sponsoring country.

DATA ANALYSIS FOR OBJECTIVE 4: DATA FROM PrEP TRIALS (3 STUDIES)

Three HIV oral PrEP studies yielded clinical data related to nevirapine and to tenofovir: Jackson's study¹²¹, Peterson's study¹²³, and Smith's study^{115, 147} (Table 4). **Smith's study** was testing tenofovir, in Botswana, between 2005 and 2007¹¹⁵. The investigators decided to terminate it, based on new "*evidence to support initiating trials of tenofovir plus emtricitabine*" - rather than testing tenofovir alone -, for HIV prevention¹⁴⁷. In March 2007, based on those new animal data, the research team closed Smith's trial (BOTUSA MB04, phase II, testing tenofovir versus placebo, in 18-29 year olds). The protocol was upgraded as Thigpen's trial, which is being conducted in the same communities and features very similar characteristics (BOTUSA MB06, phase III, testing emtricitabine/tenofovir versus placebo, in 18-39 year olds)¹⁴⁸. Seventy-one participants had been enrolled and followed up for safety, in Smith's trial, at the time of the termination¹⁴⁷. Data collected were not published and could not be released upon request, due to the "*sponsor's policies*" (February 2009: Dr. Thigpen, personal email communication; Dr. Robert Grant, personal email communication; Dr. Lynn Paxton, personal phone communication). However, it is reported in Thigpen's study protocol that no safety issues were observed in Smith's trial¹³⁶. Due to unavailability, results of Smith's trial are not further examined in this section.

Study designs and baseline characteristics of participants

Nevirapine

Jackson's study was a 3 arm-non randomized cohort, that tested 3 regimens of nevirapine (NVP, Viramune®)¹²¹. This trial, conducted in the USA, was completed as planned (no operational issues reported). Its results were published in 2003, in the *AIDS* journal, the official journal of the *International AIDS Society*¹⁴⁹.

Jackson's trial included a mixed population. Its 33 participants were over 18 years of age, both male (21) and female (12), and of different ethnicities (22 African-Americans, 8 Caucasians, 2 Hispanics, and 1 Asian). All women enrolled were African-American. Participants' higher risk factors were: having non-monogamous unprotected sex (10), being a man who has sex with men (8), having sex with an HIV-infected person (8), and using injection drug(s) and/or having sex with an injecting drug user (7). The sample included 1 hepatitis B positive person and 7 hepatitis C positive persons. No baseline data about body mass index was reported. Participants were non randomly assigned to *Cohort A* (12 participants), *Cohort B* (12 participants), or *Cohort C* (9 participants). Eight of the twelve participants in *Cohort A* were gay white males, and four of the seven hepatitis C positive participants were assigned to *Cohort B*.

Tenofovir

Peterson's randomized study tested tenofovir (TDF, Viread®) versus placebo, in high-risk women, in Cameroon, Ghana, and Nigeria¹²³. Despite the early closure of 2 of the 3 sites (Cameroon and Nigeria), data for 936 participants could be accrued - out of the 1,200 who were to contribute -. Results were published in 2007, in the *PLoS Clinical Trials* open-library journal, and have been extensively cited and commented, as they were the first available data on tenofovir from a clinical PrEP trial.

Peterson's trial included only African women who had reportedly had about 3 sex acts per week and at least 4 sex partners in the previous month. Hepatitis B infection was an exclusion criterion. The 936 participants enrolled were about 23 years (mean age). Over 90% of participants were not married and were not living with a man. 94% of the women had no more than 12 years of education. 73% had previously been pregnant and 52% were currently using some contraceptive method, 86% of those using condoms. 41% of women had had some sexually transmitted infection in the previous 6 months. (Peterson 2007, calculations based on Table 1)¹²³. Participants in the tenofovir group and in the placebo group were comparable in numbers.

HIV oral PrEP regimens tested

Nevirapine

In Jackson's trial, participants were assigned to 3 cohorts corresponding to escalated doses of oral nevirapine pills, to be taken for 12 weeks. Participants in *Cohort A* were to take 200mg nevirapine once a week, participants in *Cohort B* were to take 200mg nevirapine twice a week, and participants in *Cohort C* were to take 200mg nevirapine every other day.

Tenofovir

In Peterson's trial, participants randomized to the intervention arm were to take a 300mg tenofovir pill every day, for 12 months. Participants randomly assigned to the control arm were to take a placebo pill "*identical to the TDF tablets in size, shape, color, and taste*"¹²³.

HIV oral PrEP safety

Nevirapine

Laboratory/Pharmacokinetics. The trough level is "*the lowest level that a medicine is present in the body*" (www.wikipedia.org). Median nevirapine trough levels in blood were above 100 ng/ml, i.e., above 10 times

nevirapine's IC₅₀ (the concentration of nevirapine needed to reduce population growth of HIV by 50%, in vitro¹⁵⁰). Those levels were observed both at the first week and at the last week of on-drug follow-up, in all cohorts. However, there were large differences between the lower bound and the upper bound of the ranges of values (about 205 to 5019 ng/ml range width; Jackson 2003, calculations based on Table 4)¹²¹. Trough levels beyond 100 ng/ml - the targeted level - were not observed in all participants at all measurement time points, and nevirapine levels were not consistently detectable in some participants of Cohort A and Cohort B (Jackson 2003, Table 5)¹²¹. Also, a few participants had, intermittently, extreme levels of nevirapine (above 2000 ng/ml).

Laboratory/Hepatic function. Alanine aminotransferase (ALT), glutamyl transpeptidase (GGT), and aspartamine aminotransferase (AST) are enzymes used as biochemical markers of liver damage¹⁵¹. There was a statistically significant elevation of median GGT levels between entry and week 12, in Cohort B (from 33 to 63 IU/l, p=0.01). There was a trend towards an increase in both AST levels (15 to 28 IU/l, p=0.06) and GGT levels (21 to 38 IU/l, p=0.06), in Cohort C (highest dose tested: 200mg every other day; Jackson 2003, Table 2)¹²¹. Investigators suggested that those elevations were possibly due to outliers (two HCV antibody-positive participants and one participant with substance abuse issues) who had very high but reversible elevations. No sub-group analysis (i.e., with outliers excluded) was reported for these outcomes.

Laboratory/Participants with hepatitis. A sub-group analysis of liver enzyme values elevations was reported, for the 6 HCV antibody-positive participants analyzed (1 in Cohort A, 3 in Cohort B, 2 in Cohort C). Their median GGT elevation across cohorts (38 to 91 units, p=0.06), tended to be of greater magnitude than the elevation of that same enzyme in the whole sample, across cohorts, for the 24 participants included in the primary analysis (30 to 38 units). However, there was a notable variability in that small sub-group, with 2 participants having extreme changes (one in Cohort B and one in Cohort C; Jackson 2003, Table 3)¹²¹.

Pregnancy-related safety. *"Women of child-bearing age had to use a reliable method of birth control other than hormonal contraceptives"*. However, there was no specification about a screening process to ascertain pregnancy status of women upon enrolment. And there was no mention of a pregnancy monitoring plan during the intervention period.

Reported adverse events. The text of the report mentions that *"8 of 12 enrolled subjects in Cohort A, 5 of 12 in Cohort B, and 5 of 9 in Cohort C experienced at least one clinical adverse event (Table 1)"*, that is, 67%, 42%, and 56% in Cohort A, B, and C, respectively. However, this doesn't take into account the 7 participants who were lost to follow-up, and may have experienced unreported adverse events. Re-calculations using 24 as the denominator - the number of participants followed for safety outcomes - would yield 73%, 63%, and 71% as the respective proportions of participants who experienced at least one adverse event (8 in 11 for Cohort A, 5 in 8 for Cohort B, and 5 in 7 for Cohort C). Although the adverse events *"did not appear to increase with*

dose", 53% of those events (16 out of 30) occurred in participants in Cohort A, who were taking the lowest dose tested (200mg weekly). However, 83% of reported adverse events were graded as mild and the rest were moderate. No adverse event was attributed to the study drug.

Behavioral disinhibition. 48% of participants (16 out of 33) reportedly engaged in "*high-risk activity*" during the trial. The notion of "*high-risk activity*" was not defined, neither was the method used to assess it. For instance, it is unclear whether participants were spontaneously reporting their behaviour or whether they were specifically and systematically asked about it. Again, the denominator for this outcome measure included all 33 participants enrolled, although 7 were reportedly lost to follow-up.

Serious adverse events. Jackson *et al.* used a scale to classify laboratory adverse events (the higher the grade the more serious the toxicity). Three participants experienced a grade 3 elevation in at least one liver enzyme measured, that is, ALT > 200, ALT > 175, or GGT > 250 IU/l (international unit per litre). One of those participants also experienced a grade 4 elevation (GGT > 250 IU/l). A biologically plausible explanation was reported for two of those three participants: "*significant exposure to methylene chloride while stripping furniture*" and "*reported frequent alcohol and injection heroin use*", respectively. The third case of grade 3 elevation was not commented on, in regard to its relatedness to nevirapine.

Deaths. No death was mentioned in Jackson's report.

Tenofovir

Laboratory/Renal function. Creatinine and phosphorus are biomarkers commonly used as kidney function tests¹⁵². Peterson *et al.* also used a scale to classify laboratory adverse events (the higher the grade the more serious the toxicity). The rate of observed renal laboratory abnormalities (creatinine and phosphorus) ranged from 0.0 to 8.3 per 100 person-years, in the tenofovir group. It was between 0.0 and 10.4 in the placebo group. Despite lower rates of grade 1 and grade 2 laboratory abnormalities, in the tenofovir group (rate ratios of 0.5 to 0.9), there was no statistically significant difference between groups, whatever the grade (Peterson 2007, Table 2)¹²³. No kidney-related abnormal laboratory value caused any participant to withdraw from study nor caused the investigators to withdraw any participant.

Laboratory/Hepatic function. The rate of observed hepatic laboratory abnormalities (AST and ALT elevation) ranged from 0.0 to 17.8 per 100 person-years, in the tenofovir group. It was between 0.0 and 13.5 in the placebo group. Despite some higher rates of grade 1 and grade 2 laboratory abnormalities in the tenofovir group (rate ratios of 0.7 to 1.5), there was no statistically significant difference between the tenofovir group and the placebo group, for either elevation of AST or ALT, whatever the grade (Peterson 2007, Table 2)¹²³. No

liver-related abnormal laboratory value caused any participant to withdraw from study nor caused the investigators to withdraw any participant.

Laboratory/Rebound hepatitis flare. The study team amended its protocol (in August 2005) to allow for assessment of hepatitis B flares (after tenofovir discontinuation), based on newly available evidence¹²³. This applied only to participants in the Ghana site, as the intervention had been halted in the other 2 sites by then. 56 participants tested positive for HBsAg (hepatitis B surface antigen) at last visit. Four grade 1 ALT/AST abnormalities were observed (1/23 participants in tenofovir group and 3/33 participants in placebo group), within the 3 months of follow-up after drug discontinuation. The relative risk was 0.5 (statistic derived from absolute event frequencies and denominators reported)¹²³.

Pregnancy-related safety. Pregnancy/breastfeeding was an exclusion criterion in Peterson's study. Participants were tested for pregnancy at every monthly visit. The reported pregnancy rate, during the follow-up period, was 52/100 person-years. No information was found, in the report, about safety outcomes in pregnant participants or in their foetus/infants. It is not specified whether seroconverters in the tenofovir group were pregnant or not.

Reported adverse events. Overall, 74% of participants analyzed for adverse events reported at least one adverse event during the follow-up period (75% in the tenofovir group, 72% in placebo group). Among the top ten complaints reported, seven were slightly more frequent in the intervention group than in the control group: abdominal pain, flatulence, anorexia, headache, dizziness, urinary tract infection - not otherwise specified -, and vaginal candidiasis. However, no differences were statistically significant, based on system organ subgroup analyses and on analysis of the subgroup of participants positive for hepatitis B surface antigen. No adverse event caused any participant to withdraw from study.

Behavioral disinhibition. The overall average of self-reported number of weekly coital acts went from 12 (at screening) to 15 (throughout follow-up). However, the overall average of self-reported number of sexual partners over the previous month went from 21, with an average of 11 new partners (at screening) to 14, with an average of 6 new partners (throughout follow-up). And the self-reported condom use during last coitus went from 52% (at screening) to 92-95% (throughout follow-up). Greg Guest et al. published a separate article reporting details on behavioural outcomes, restricted to participants in Ghana. They noted variations among participants, regarding behavioural changes, with some participants having "*unique risk profiles*"¹⁵³.

Serious adverse events. Among the participants analyzed for serious adverse events, the overall rate of serious adverse events was 2.6% (2.1% in tenofovir group, 3.0% in placebo group). This difference was not statistically significant, and none of those events were deemed related to study drug.

Deaths. The 2 deaths reported occurred in Cameroon, during the off-product follow-up period, and were deemed unrelated to study drug. One deceased participant (induced abortion) was in the tenofovir group; the other one (anaemia-related problem) was in the placebo group.

HIV oral PrEP efficacy

Nevirapine

Efficacy evaluation was not listed among the objectives of Jackson's study but participants were tested 4 weeks after their last dose. No HIV seroconversion was observed in the 24 participants analyzed.

Tenofovir

HIV-1 and -2 antibody seroconversion was monitored monthly throughout the follow-up period. Eight seroconversions were observed, all occurring *"early in the follow-up period"*. These included two participants taking tenofovir (0.86 /100 person-years) and six participants taking placebo (2.48 /100 person-years). Both groups contributed a comparable amount of data to the analysis (232.6 person-years for the placebo group, 241.3 person-years for the placebo group). Although the rate ratio of reduced likelihood for HIV infection was of 0.35, favouring tenofovir, the difference was not statistically significant ($p=0.24$). Six more women from Cameroon seroconverted during an extended off-product follow-up. Four had been randomized to the tenofovir group and two to the control group (delay after last product dose and person-years contributed were not specified).

Adherence / compliance to HIV oral PrEP

Nevirapine

In the *Methods* section of the report, it is stated that participants *"orally self-administered a 200mg tablet"* of nevirapine according to their assigned regimen and that the *"tablets were provided in sufficient quantity in blister packs labelled with the study dose"*. It is also said that study *"visits were scheduled so that subjects were able to take their next dose of nevirapine during the study visit, (...) allowing administration of study drug to be directly observed during those study visits."* Hence, based on the report, it appears that *directly observed therapy* was to be used, which is essential for trough level measurement. In the *Results* section, though, it is reported that some subjects *"had nevirapine trough levels that varied by more than fivefold, which (...) suggested poor adherence and/or variable dosing in some subjects."* So, if *directly observed therapy* was used, it seems that it was not applied consistently. There is no mention of any other outcome measure for

adherence assessment. The overall withdrawal rate was 27% and increased with dose: 8% in *Cohort A*, 33% in *Cohort B*, and 44% in *Cohort C* (Jackson 2003, calculations based on text)¹²¹.

Tenofovir

As a measure of adherence, the study report gives the ratio of the number of pills not returned over the total number of days in the effectiveness analysis. It was so found that, overall, 74% of dispensed pills had not been returned, excluding off-product time due to pregnancy. The overall attrition rate was 63%: 62% in the placebo group and 64% in the tenofovir group. Not surprisingly, the withdrawal rate varied by country involved: 59% in Cameroon (site closed early, after all participants were enrolled, due to public controversy), 23% in Nigeria (site closed early, after partial enrolment, due to protocol violations), and 18% in Ghana (follow-up as planned) (Peterson 2007, calculations based on Figure 1)¹²³.

Considerations for resistance

Nevirapine

No testing for resistance was mentioned in Jackson's report *Methods* section and no "breakthrough" HIV infection was detected during follow-up¹²¹.

Tenofovir

Only one of the two participants who seroconverted under the tenofovir regimen got her blood tested for resistance. A standard genotypic analysis showed no evidence of mutant virus selection¹²³.

HIV oral PrEP acceptability

No measure of acceptability was reported in source documents reviewed, for either nevirapine or tenofovir.

6.4. QUALITY ASSESSMENT

QUALITY OF REPORTING

Trial registry files

Thirteen of the 16 studies included were found in a trial registry. The delay between the registration date ("*First received date*" field, in the NIH registry) and the "*Start date*" was between -12.4 months (registration date *before* planned start date) and +13.8 months (registration date *after* reported start date), with a mean of -1.8 months. The start date preceded the registration date for only four registered studies. One registered study had no start date displayed and another study had no end date displayed.

Protocols

The 12 approved protocols and the one study summary - used in lieu of inexistent approved protocol - were dated between 2 June 2004 and 07 April 2009; no date was found for one of the protocols. The protocol versions varied from a draft version to a version 7.0. The study summary was a draft; six protocols were version 1.x, one was version 2.0, three were version 3.x, one was a version 4.0, and one was a version 7.0. The text length of the protocols reviewed ranged from 38 to 117 pages, with a mean of 89 pages (excluding the 2 page-study summary). The number of references listed ranged from 8 to 92, with an average of 50 (no reference cited in the study summary). The only systematic review identified, in one of the reference lists, was about the effect of contraceptives on bone mineral density¹⁴¹. Ten study teams mentioned between 1 and 8 other HIV oral PrEP trials. The most cited trial was Peterson's (in 6 other protocols); followed by Choopanya's (in 5 other protocols); Thigpen's and Grant's (in 4 other protocols); Grohskopf's, Celum's and Van Damme's (in 3 other protocols); Page-Shafer's and Chirenje's (in 2 other protocols); and Jackson's and Smith's (1 other protocol). Four trials were mentioned in no other protocol: Hendrix, Anton, Grosskurth, and Hosek.

Consent forms

Consent forms were obtained and analyzed for 11 of the 14 studies ethically appraised. All eleven study teams had more than one type of consent forms or distinct consent blocks within consent form reviewed. Ten studies had a consent process for screening, eleven had one for enrolment, and eight had one for storage/future use of human samples. Three teams had a consent process for significant related persons (i.e., sexual partners or parents/guardians), and four had one for HIV testing. For practical purposes, only *enrolment* consent forms were analyzed. The length of the text of those consent forms was between 2,126 and 8,166 words, with a mean of 4,812 words. The average number of words per sentence was between 8 and 19, with a mean of 12.

Consent forms' content

Eleven of the twelve consent forms obtained were appraised: Anton's consent form was excluded due its focus on a rectal microbicide¹⁴⁴. The percentage of UNAIDS requirements mentioned in the enrolment consent forms was between 47 and 94 %, with a mean of 77%. Five of the 17 items based on the UNAIDS guidelines ([Attachment 4](#), section 4: *items # 2, 5, 6, 8, 11*) were consistently mentioned in all consent forms; these items read as follows:

"experimental nature of the biomedical HIV prevention product"

"provision of counseling concerning risk reduction of HIV exposure"

"access to risk-reduction means"

"specific risks for physical harm"

"potential referral services should harm occur".

None of the items was consistently missing in all studies. Items related to the management of personal data were the least commonly found: for only 2 studies ([Attachment 4](#), section 4: *items # 16 and 17*). The *"nature and duration of available care and treatment"* ([Attachment 4](#), section 4: *item # 12*) was specified in 5 of the consent forms analyzed. Other items were found in 6 to 10 of the consent forms reviewed.

Study reports

Published study reports were retrieved for 3 of the 16 trials included: Jackson¹²¹, Page-Shafer¹²², and Peterson¹²³. In the TREND statement¹⁰³, **Jackson's** report (non randomized clinical trial) completely fulfilled 10 domains (out of 22), with four presenting one non applicable "bullet point". Incomplete information was found for the 12 following domains: *Title and abstract, Participants, Outcomes, Assignment method, Blinding, Results, Recruitment, Baseline data, Baseline equivalence, Outcomes and estimation, Adverse events, and Generalizability*. Overall, 27 out of the 46 "bullet points" were fulfilled, and one was unclear. The quality of reporting for **Page-Shafer's** randomized trial was not assessed for quality. That study was terminated before the enrolment phase; it produced no results, and its report summarized only operational issues¹²². In the CONSORT statement¹⁰², 21 of the 22 checklist items were found for **Peterson's** study (randomized trial). One criterion was incompletely fulfilled (# 11), as blinding was appropriately described but there was no mention of a method to evaluate the success thereof.

STANDARD QUALITY ASSESSMENT

I could determine the Jadad score¹⁰⁴ of 15 of the 16 studies included (Hosek's study had no target source document available). Clinical data were available for only two studies^{121, 123}. The other 13 studies analyzed for methods were assessed based on their trial registry file or their protocol. Overall, Jadad scores were between 1 and 5, with ten of the fifteen studies (67%) getting a score of 3 or more.

Jackson's study was also assessed using the *Newcastle-Ottawa Quality Assessment Scale*¹⁰⁵, as it was a non randomized study. I gave it 7 stars, out of 9 (4/4 for *selection*, 1/2 for *comparability*, 2/3 for *outcome*). The report presented a sub-group analysis of hepatitis C positive participants. However, a point was lost for *comparability* because the study did not control for body mass index (factor considered most important) and incompletely described the gender composition of the groups. Another point was lost for *outcome/adequacy of follow up of cohorts* because the follow up rate was higher than 15% (maximum rate considered adequate).

6.5. ADDITIONAL ANALYSES

SUB-GROUP ANALYSES

HIV oral PrEP trials with at least 3 source documents

Eleven included studies had 3-4 target source documents available (trial registry file, protocol, enrolment consent form). Two of those had also a report available. All eleven studies were among the 14 ethically appraised. The 3 studies appraised that had 1- 2 source document(s) were the outliers identified in the primary ethics analysis (three lowest ethics scores). Nine of the 11 studies with 3-4 source documents (82%) had a Jadad score of 3 or more ([Figure 5](#)). The median ethics score was 58% (higher than corresponding value for trials with 1-2 sources available). Median ethics sub-scores were between 43% (*Principle 2: social value*) and 75% (*Principle 5: favorable risk-benefit ratio* and *Principle 7: informed consent*). All median proportions were higher than corresponding values for studies with 1-2 source document(s) available ([Figure 6](#)).

HIV oral PrEP trials hosted outside of the USA

Out of 15 studies analyzed for methods, 3 involved the USA alone (2 were ethically appraised), 2 involved countries including the USA (both were ethically appraised), and 10 involved countries other than the USA (all ethically appraised). Trials with sites only in the USA have a total of 451 participants, mostly men having sex with men; they are phases I to II studies. Trials with sites in and outside the USA have a total of 3,144 participants, mostly men having sex with men; they are phases II and III studies. Trials with no site in the USA have a total of 16,757 participants (excluding those never enrolled^{108, 109}). Those studies included all PrEP target populations previously identified, and they are mostly phases II to III studies (only 1 phase I/II) ([Table 3](#)).

Eight of the ten trials with no site in the USA had 3-4 source documents available; all ten studies were ethically appraised. Eight of those ten trials (80%) had a Jadad score of 3 or more ([Figure 5](#)). The median ethics score was 60% (higher than corresponding value for trials with at least one USA site). Median ethics sub-scores were between 45% (*Principle 6: independent review*) and 75% (*Principle 4: fair selection of study population* and *Principle 5: favorable risk-benefit ratio*). Most median proportions were equal to or higher than corresponding values for studies with at least one site in the USA. The exception was *Principle 6 (independent review)* whose median ethics sub-score was lower ([Figure 7](#)).

HIV oral PrEP trials focusing on efficacy/effectiveness

Nine of the 15 studies analyzed for methods had efficacy or effectiveness as a primary outcome ([Table 5](#)). They all had 3-4 source documents available and were all ethically appraised. Eight of those 9 studies (89%) had a Jadad score of 3 or more ([Figure 5](#)). The median ethics score was 61% (higher than corresponding value for trials not focusing on efficacy/effectiveness). Median ethics sub-scores were between 50% (*Principle 1: collaborative partnership*) and 83% (*Principle 4: fair selection of study population* and *Principle 7: informed consent*). All median proportions were higher than corresponding values for studies not focusing on efficacy/effectiveness ([Figure 8](#)).

HIV oral PrEP trials closed early

Four of the 15 studies analyzed for methods were partially or fully closed before the planned end date, not based on a scientific interim analysis ([Table 2](#)). Three of those four studies had 3-4 source documents available and all four studies were ethically appraised. All 4 studies (100%) had a Jadad score of 3 or more ([Figure 5](#)). The median ethics score was 53% (lower than corresponding value for trials not closed early). The median ethics sub-scores ranged between 35% (*Principle 1: collaborative partnership*) and 67% (*Principle 7: informed consent*). Half sub-scores were lower than the corresponding values for trials not closed early: *Principle 1 (collaborative partnership)*, *Principle 3 (scientific validity)*, *Principle 4 (fair selection of study population)*, and *Principle 6 (independent review)* ([Figure 9](#)).

CORRELATION BETWEEN ETHICS CONSIDERATIONS AND STUDY QUALITY

For the 14 studies ethically appraised, Jadad scores did not increase with increasing ethics scores ([Figure 10](#)).

EXPLORING HETEROGENEITY

The three studies with the lowest ethics scores also happened to be the three for which only 1 to 2 source document(s) was/were available. **After removing those 3 outliers from the primary analysis**, the median ethics score increased to 58% (IQR=[51-68] %). The lowest median ethics sub-score remained for *Principle 2: social value* (43%). However, the highest median ethics sub-scores were then for *Principle 5: favorable risk-benefit ratio* and *Principle 7: informed consent* (75%). All proportions were equal to or higher than their corresponding value in the original primary analysis ([Table 11](#)). All time trends remained positive, except for *Principle 8: respect for recruited participants and study community* (slightly negative slope).

After removing the 3 outliers from the sub-group analysis based on host region (trials with no USA site versus trials with at least one USA site), the median ethics score increased to 63%. The median ethics sub-scores ranged between 50% (*Principle 1: collaborative partnership*) and 83% (*Principle 4: fair selection of study population*). Most proportions were equal to or higher than the corresponding values for the studies with at least one USA site. Like in the original sub-group analysis, the exception was *Principle 6 (independent review)* whose median proportion of ethics considerations reported was lower ([Table 11](#)).

After removing the 3 outliers from the sub-group analysis based on the primary question (efficacy/effectiveness trials versus non efficacy/effectiveness trials), the median ethics score remained 61%. The median ethics sub-score remained between 50% (*Principle 1: collaborative partnership*) and 83% (*Principle 4: fair selection of study population* and *Principle 7: informed consent*). Those proportions remained the same because none of the outliers were efficacy/effectiveness trials. All proportions also remained equal to or higher than the corresponding values for the studies not focusing on efficacy/effectiveness ([Table 11](#)).

After removing the 3 outliers from the sub-group analysis based on study status (trials partially or fully closed early versus trials not closed early), the median ethics score increased to 65% (higher than corresponding value for trials not closed early). The median ethics sub-scores ranged between 50% (*Principle 1: collaborative partnership*) and 100% (*Principle 4: fair selection of study population*). Two of those proportions remained lower than the corresponding values for trials not closed early: *Principle 3 (scientific validity)* and *Principle 6 (independent review)* ([Table 11](#)).

After removing the 3 outliers from the time trends analysis, trends for ethics scores and Jadad scores remained positive, although the regression line slope for Jadad scores had a smaller magnitude ([Figure 11](#)).

6.6. SYNTHESIS OF RESULTS

SUMMARY FOR OBJECTIVE 1: IDENTIFICATION OF PrEP TRIALS

I identified 16 HIV oral PrEP clinical controlled trials: 2 completed and published, 3 halted, 6 ongoing, and 5 in planning, all within the past ten years. Sample sizes vary between 18 and 4,200 participants. Trials are to involve about 20,451 heterosexual men/women, men having sex with men, injecting drug users and serodiscordant couples, in at least 17 countries (mostly in Africa, but also in Latin America, South-East Asia and North America). Pills tested have been nevirapine, tenofovir and emtricitabine/tenofovir. Fifteen studies included safety, efficacy/effectiveness, and/or adherence as primary outcome measures, and twelve are advanced trials (phases II through III). Seven trials were designed with multinational sites (Figure 12). All trials have USA-based lead investigators and are sponsored by at least one USA-based institution (Table 7).

SUMMARY FOR OBJECTIVE 2: METHODS IN PrEP TRIALS

Fifteen of the sixteen HIV oral PrEP studies included were designed as randomized trials. The estimates of HIV incidence rate (2.0/100 persons-year and up) and of the hypothetical pill efficacy (55% and up) used for sample size determination vary across studies. Both continuous and intermittent regimens are being tested, for typical follow-up durations of 12 months or more. HIV testing is generally done monthly to monitor serostatus. All study teams analyzed reported provision of some behavioural HIV prevention co-interventions to all enrolled participants, as well as some monitoring of adherence. Outcome measures for physical/physiological safety are usually well defined, unlike psychosocial adverse events (especially social events). Still, 13 study teams report some care plan for the management of adverse events during trial. Overall, 10 out of 15 studies analyzed for methods (67%) had a Jadad score of 3 or more.

SUMMARY FOR OBJECTIVE 3: ETHICS APPRAISAL OF PrEP TRIALS

In the primary analysis, the median ethics score was 56%; this average slightly increased (58%) when the analysis was restricted to studies for which a full protocol was available. At the principle level, the median ethics sub-score was lowest for *Principle 2: social value* (31%), even after outliers were removed (43%). When

all 14 appraised studies were included, the median ethics sub-score was highest for *Principle 4: fair selection of study population* (67%); but it was for *Principle 5: favourable risk-benefit ratio* (75%) and *Principle 7: informed consent* (75%) when outliers were excluded from analysis. In the sub-group analyses (based on source documents available, on host countries, on primary question and on study status), the lowest median proportion of ethics items reported tended to be for *Principle 1 (collaborative partnership)*; and the highest median proportion of ethics items reported tended to be for *Principle 4 (fair selection of study population)* (Table 11).

SUMMARY FOR OBJECTIVE 4: DATA FROM PrEP TRIALS

I identified four studies that yielded some data: Jackson (completed)¹²¹, Peterson (completed after 2 out of 3 sites were prematurely closed)¹²³, Page-Shafer (halted before enrolment)¹²², and Smith¹¹⁵. **Jackson's** phase I/II trial, tested 3 infra-therapeutical regimens of nevirapine, for 12 weeks, and was conducted in the United States of America. The study report mentioned no operational issues¹²¹. Primary outcomes were safety, tolerability, and pharmacokinetics. The investigators concluded that all tested regimens were safe to use (no statistical difference across groups for laboratory and clinical adverse events). Although there was no focus on efficacy/effectiveness, no HIV seroconversion was observed. The results might have been biased by an imbalance of potential confounders (non randomized study, no adjustment for body mass index) and a high withdrawal rate (27% overall), particularly in the group taking the highest dose (44%). The generalizability of those results is limited due to the small sample size ($n=33$), a mixed population and a relatively short follow-up (12 weeks). **Peterson's** phase II trial was conducted in Ghana, Cameroon and Nigeria, with the latter 2 sites closed prematurely¹²³. However, the Ghana site could collect data of that country's participants as planned; those results were analyzed along with incomplete data accrued in Cameroon and Nigeria. The investigators concluded that the daily tenofovir regimen tested was safe to use (no statistical difference across groups for laboratory and clinical adverse events) but the results might have been biased by a very high attrition rate (63% overall), mainly due to early closures. Consequently, the study was not powered enough to allow conclusions on efficacy. There were 2 HIV seroconverters in the tenofovir group versus 6 in the placebo group ($p=0.24$). **Page-Shafer's** study did not accrue any data, as it was halted before enrolment. The report discussed operational issues faced by study team¹²². Seventy-one participants were followed in **Smith's** trial¹⁴⁷ that tested tenofovir versus placebo, before it was prematurely terminated. It was upgraded to Thigpen's trial^{147, 148}, a phase III study testing emtricitabine/tenofovir. There was reportedly "*no evidence for safety issues*" in the 71 participants who contributed data¹³⁶. However, those data have not been published and could not be released upon request.

Consequently, the only data available are those from Jackson's study and Peterson's study. But those studies are different in many aspects. Jackson's study tested nevirapine (a nonnucleoside-based reverse transcriptase inhibitor), in a mixed population. And Peterson's study tested tenofovir (a nucleotide reverse transcriptase inhibitor), in women. Moreover, Jackson's trial was a quasi-experimental study (3 arm open-label cohort) while Peterson's trial was an experimental study (2 arm-randomized double-blind clinical trial). Because of those critical differences and due to the paucity of available data, **a metanalysis was not conducted**.

6.7. RISK OF BIAS ASSESSMENT

The risk of bias was assessed for the studies that had at least one target source document available (15 analyzed for methods, 14 studies also ethically appraised). Allocation sequence was appraised as adequately generated for 3 studies, not appropriate for 1 study, and unclear for 11 studies. Allocation was appraised as adequately concealed for 9 studies, not appropriate for 3 studies, and unclear for 3 studies. Allocation concealment during study was appraised as appropriate for 8 studies, not appropriate for 1 study, and unclear for 6 studies. Incomplete outcome data was appraised as adequately addressed for 7 studies, not adequately addressed for 7 studies, and not clearly addressed for 1 study. Selective outcome reporting was appraised as unlikely for 1 study, unclear for 1 study, and not applicable for 13 studies.

At the study level, eight key other risks of bias were identified. Potential selection biases identified included: self-selection of participants (e.g., potentially highly motivated), misclassification through sub-optimal testing for baseline HIV serostatus (e.g., absence of testing to confirm positive results, lack of consideration for HIV infection window period), and misclassification through sub-optimal assessment of baseline HIV exposure (i.e., non standard questionnaire). Potential ascertainment biases identified included: sub-optimal measurement of safety outcomes (e.g., unclear measures for risk-taking behaviours), sub-optimal measurement of efficacy/effectiveness outcomes (e.g., single test, lack of consideration for HIV infection window period), sub-optimal compliance (e.g., absence of adherence counselling), sub-optimal adjustment for confounders (e.g., no mention of analyses controlling for key co-factors), and undisclosed conflicts of interest (e.g., institutional review board, sponsors) ([Table 12](#)).

At the outcome level, for safety, the risk of bias was deemed high for 1 study (high withdrawal rate), low for 6 studies (e.g., monitoring of multiple dimensions of risk, both objective and subjective outcome measures), and unclear for 8 studies (e.g., behavioural prevention below standard, unclear safety outcome measures). At the outcome level, for efficacy/effectiveness, the risk of bias was deemed low for 8 studies (e.g., testing algorithm with confirmatory tests, consideration for window seroconversion period), unclear for 1 study (high attrition rate) and not applicable for 6 studies (no focus on efficacy/effectiveness). However, studies that are more recent and with larger sample sizes are randomized, and their investigators tended to report more of the aforementioned methodological considerations. Hence, the risk of bias *across studies* was judged as low, both for safety assessment and for efficacy/effectiveness assessment ([Table 13](#)).

7.0 DISCUSSION

7.1. DISCUSSION ON OBJECTIVE 1: IDENTIFICATION OF PREP TRIALS

A total of 16 clinical studies were identified, all initiated within the last 10 years. My review's eligibility criteria were purposefully inclusive so as to locate *"any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes"*¹⁵⁴. A few other publications reported lists of 3 to 12 oral PrEP studies, most based on non systematic or unspecified search strategies^{15, 70, 155-159} ([Appendix 7](#)). The only systematic review I am aware of was published in January 2009 by Charles Okwundu and Christy Okoromah, in the Cochrane Library⁷⁷. No data were pooled because authors could include only one study (Peterson)¹²³. Authors of that systematic review identified but excluded Jackson's study, and they reported a list of 8 ongoing or planned PrEP studies - all identified by my review -. The fact that I was able to identify more studies shows that a systematic search across multiple types of information sources can improve retrieval of trials, especially for research in progress like HIV oral PrEP. The requirement by editors for trial registration⁸¹, the collaboration of PrEP investigators, and the availability of some recent protocols on sponsor's website were significant facilitators. This review of PrEP trials appears to be the most comprehensive, to date.

The number of HIV oral PrEP studies has been growing. Based on study documents reviewed, the number of HIV oral PrEP concomitantly active was between 0 and 2 in 2002-2004, between 4 and 6 in 2005-2008, and it went up to 11 in 2009. In spite of initial difficulties (safety issues with nevirapine study, early closure of tenofovir study sites in 2004, 2005 and in 2007), the PrEP field seems to be expanding. Possible triggers to the rise of PrEP research include the approval of tenofovir (2001), considered safer and more potent than many antiretrovirals previously used¹⁶⁰. Other influences may be the negative results from other biomedical HIV prevention research fields, such as vaccine research (e.g., Merck's STEP trial in 2007)¹⁶¹, microbicide research (e.g., phase III PRO2000 in 2009)¹⁶², and infectiousness control (e.g., partners in prevention trial)²⁷. What is certain is that PrEP funding has been exponentially increasing. Indeed, it is estimated that a cumulative 119 million US dollars has been invested in HIV PrEP research, soaring from less than 2 million in 2002 to over 44 million in 2008^{80, 163}. Time will tell if the marginally positive results from the Thai HIV vaccine trial¹⁶⁴ will affect the interest and support granted to PrEP over the past few years.

HIV oral PrEP research has the potential to answer several important questions. Primary questions reported in protocols address not only how safe or efficient PrEP might be but also other important outcomes such as adherence and acceptability. The overall risk of bias is low, as most studies are large randomized

trials. And diverse populations are studied; so, PrEP trials results should be applicable to a variety of groups.

Heterosexual women are the population most commonly included in HIV oral PrEP studies (in 12 of 16 studies). I could easily find information about study population in all types of documents I reviewed (trial registry files, protocols, consent forms, study reports). This massive inclusion of females in PrEP trials addresses concerns that women have traditionally been under-represented in clinical trials^{47, 165}. Moreover, women in sub-Saharan Africa are disproportionately affected by HIV, representing about 60% of the cases there¹⁶⁶. A common argument to support HIV oral PrEP research is that it might help empower women who, for social and cultural reasons, may have challenges in negotiating use of condom with their sexual partners¹⁶⁶. Thus, the results of most PrEP trials will surely be applicable to women.

Still, many protocols include men (11 out of 16 studies). PrEP study documents report that heterosexual males have been enrolled in studies, essentially in mixed groups (e.g., with women) whereas *men who have sex with men* (MSMs) are usually enrolled in distinct trials. Sexual intercourse is known to be the major mode of transmission of the HIV infection, globally. And receptive anal sexual contacts are estimated to be five times riskier than receptive penile-vaginal contacts, which might mean even more risk for receptive MSMs compared to women in heterosexual couples¹⁶⁷. Participation of men in HIV prevention trials could be an opportunity to raise their awareness on the role they may play in minimizing transmission.

Other populations targeted in HIV oral PrEP trials include injecting drug users and serodiscordant couples. Both those populations were found to be studied in distinct efficacy trials. Dependence to addictive substances and related socioeconomic issues can easily hinder the capacity to adopt safer behaviours in regards to recommendations for HIV prevention (e.g., exclusive use of clean equipment). Percutaneous needle stick and needle-sharing injection-drug use are among the top 4 riskiest behaviours identified by the United States *Centers for Disease Control and Prevention* (CDC). Estimated per-act risk for those behaviours ranges from 30 to 67 infections per 10,000 exposures¹⁶⁷. Hence, the more frequent the exposure, the higher the transmission risk. As for seronegative heterosexuals whose partners live with HIV, they are in a somewhat similar situation: they are clearly exposed to HIV, with a high risk of infection. So, they are strongly advised to minimize that risk by adopting safer sex measures. But once an exclusive sexual relationship becomes stable, partners may choose to stop using condoms, especially if they want to have children. It has been previously suggested that it is possible to prevent infection while allowing pregnancy using “timed PrEP”. In at least one small non-controlled cohort study, HIV transmission was prevented while conception occurred in 71% couples, following the prescription of tenofovir shortly before sexual intercourse¹⁶⁸. Thus, if adequately powered trials can confirm the efficacy of oral antiretroviral therapy in injecting drug users and in serodiscordant couples, it could help slow down the spread of the infection, and improve the quality of life in populations with clearly identified exposure to HIV.

At least 12 of the 16 PrEP studies were designed to be conducted in low and middle income countries, with 11 sub-Saharan African countries involved. Sub-Saharan Africa is the region of the world most heavily hit by the HIV/AIDS pandemic, with about 67% of cases². South and South-East Asia, Latin America, and North America are among the top five regions with the highest prevalence, with estimates of 4.2, 1.7, and 1.2 million adults and children living with HIV in 2007, respectively². It might make sense to enrol into trials members of communities in high prevalence areas who might benefit the most from tested interventions, if these are proven safe and effective. However, HIV oral PrEP studies tend to be led and funded by institutions from industrialized countries. This potentially creates situations of power imbalance, which, in turn, may increase the risk of exploitation and other kinds of issues, such as conflicts of interest (e.g., at the level of the sponsors, of the local administrators, of the investigators, of the ethics review board members). So, it is crucial to design and monitor the studies in a culturally sensitive way, in order to insure that local communities really benefit from PrEP trials.

Interestingly, HIV oral PrEP research is essentially financed by American institutions. Trial registry forms, protocols and reports reveal that nine American public and private institutions have been providing material support for all HIV oral PrEP trials. It is worth noting that *Gilead Sciences Inc.* contributes in-kind donations (pills and placebo pills) to most studies. This is the company that manufactures both tenofovir and tenofovir/emtricitabine, the two pills currently tested for PrEP. Although Gilead is not the biggest sponsor in cash value¹⁶⁹, this level of involvement suggests an obvious interest of that company in determining whether its products can be used for a new indication.

Only six HIV oral PrEP studies have had locals as co-lead investigators. Although most study documents reviewed mention locals as collaborators (e.g., staff for implementation of procedures), only a few teams report having locals in a top leading position. Irrespective of this, some protocol teams demonstrate a deep knowledge of and extended experience in host communities, and some do provide solid references to support the relevance of conducting trials in certain communities. Still, this leadership scheme suggests some imbalance in empowerment between research initiators and local partners.

What role does the industry play in HIV oral PrEP research?

Most HIV oral PrEP studies were designed to test tenofovir and/or emtricitabine/tenofovir, two antiretrovirals manufactured by *Gilead Sciences, Inc.*, an American pharmaceutical company (www.gilead.com). That same company is cited as a sponsor, an in-kind provider or a collaborator by 13 study teams, and it has reportedly contributed over a million US dollars to PrEP research in 2007 alone⁸⁰. In Peterson's study report, an employee and shareholder of Gilead is cited as an author (competing interests declared), and as having contributed to the study design¹²³. Further public discussion is necessary about perceived, potential and real conflicts of interest on Gilead's part, considering the level of involvement of that company.

Why are more advanced HIV oral PrEP trials conducted in resource-limited countries?

Over 80% of PrEP study participants are to be enrolled in resource-limited host countries, into more advanced trials, while studies restricted to the USA are to contribute less than 3% of the participants, into smaller studies. Why such a striking difference? High prevalence in poorer communities does not seem to be a robust justification since, in any case, very few seroconversions are expected to occur during trials - partly due to concomitant behavioural prevention^{85, 153}. Are developing countries carrying more than their share of the burden of PrEP research?

No clear justification was found regarding the decision to conduct trials in resource-limited communities *rather than* in an industrialized country. While some investigators have presented arguments to justify the choice of a resource-limited community (e.g., high prevalence, local political agenda for HIV biomedical prevention), one may see exploitation in such choices (e.g., lower operational costs, weaker local regulations, higher corruptibility of administrators, undue inducement of participants and of local collaborators). Indeed, repeatedly in history, harm has been done in the name of research¹⁷⁰.

Overt examples of abuse in clinical research include atrocities inflicted on Jews, Romani people and political prisoners by Nazi physicians (1939-1945) as well as denial of available treatment by Alabama doctors who followed poor African-American men suffering from syphilis in Tuskegee (1932-1972)¹⁷⁰. More recently and closer to PrEP research, some HIV trials for the prevention of vertical transmission were deemed unethical. Those trials were sponsored by the USA *National Institutes of Health* and the *Centres for Disease Control and Prevention* (CDC). They tested zidovudine (AZT) versus a placebo and with no provision of behavioural prophylaxis, in African pregnant women living with HIV. At that time, though, AZT had already been established as the standard of care to prevent mother-to-child HIV transmission⁷⁶. Commenting on those studies, Angell said, back in 1997:

*"The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives. To survive, it is necessary to get the work done as quickly as possible, with a minimum of obstacles. When these considerations prevail, it seems as if we have not come very far from Tuskegee after all."*⁷⁶.

Similar concerns have been expressed for HIV oral PrEP research. They may be based on popular reminiscence of historical misconducts of clinical researchers¹⁷¹ and on disbelief that the trial will actually benefit participating communities. Ensuing mistrust may be long-lasting and may work against research efforts, even well-intended ones¹²².

If PrEP works, who would be eligible for it?

So far, HIV PrEP research has considered a wide age range (up to 65 years) in diverse key populations at higher risk^{1,8}, but only healthy adults. However, most recent global updates on the HIV/AIDS epidemic show that young sexually active adults (15-24 years old) are also at a high risk of getting infected, representing 45% of the new infections². Also, some clinical conditions, considered as exclusion criteria in PrEP studies, are common in the populations targeted by this approach (e.g., tuberculosis, pregnancy). Hosek's feasibility study will possibly be followed by a bigger trial with adolescents (i.e., younger than 18 years old)¹²⁶. Further bridging studies will also be needed to complement the results of on-going studies to assess the value of PrEP in individuals with common medical conditions¹⁵⁸.

Another issue is that the inclusion criteria defining the level of risk vary widely, across HIV oral PrEP trials. For the rate of sexual acts, for instance, one study required participants to have had a minimum of 2 consensual receptive anal sexual acts within the previous 12 months whereas another study required as many as 3 sexual acts *per week*. Moreover, the baseline level of risk is likely not constant. After enrolment, trial participants may engage in more risk-taking behaviours (e.g., due to behavioural disinhibition) or reduce their level of risk (e.g., following intensive counselling provided throughout the study)¹⁵³. Clinical practice guidelines will need to be developed to specify the profile of patients who could/should be prescribed PrEP.

If PrEP works, how would it be rolled-out?

As for any type of clinical research, the ultimate goal of PrEP research is to have antiretrovirals used for HIV prevention in routine clinical practice. Should the target population be restricted to members of key populations at higher risk (reservoirs)? If so, how will decision makers present the relevance of providing possibly marginalized persons (e.g., sex workers, injecting drug users) with drugs that remain inaccessible to way too

many people living with HIV, even in richer countries¹³¹? Should *any* sexually active person be entitled to PrEP? If so, it will require thoughtful planning and monitoring of huge public health programmes.

Unlike microbicides or vaccines, HIV antiretrovirals are already approved by regulatory agencies and they are available on the market for therapeutic indications. Some media reports^{172, 173}, some surveys¹⁷⁴⁻¹⁷⁶, and a case report¹⁷⁷ suggested that antiretrovirals have already been both used by and prescribed to persons at higher risk of HIV infection. Based on these publications, off-label use of antiretrovirals (for HIV prophylaxis) seems to remain uncommon despite a certain level of awareness of the HIV oral PrEP concept, in some American communities. However, those few studies have limitations and may not reflect the extent of the phenomenon. “Underground” PrEP use (e.g., “party drug”, drug sharing/selling by HIV patients) could increase if trials confirm that it actually works.

Whether persons targeted for PrEP are the general population or a sub-group thereof, public information will need to be adequately packaged and delivered. Even though HIV oral PrEP is a quite simple concept, efficiently explaining all its implications is not an easy task. One argument to justify PrEP research is that the behavioural approach is not feasible or acceptable for some people. But for optimal efficacy, PrEP will still need to be used in combination with behavioural strategies... Also, currently, many people, especially in areas of high HIV prevalence, do not even know their HIV status, either because of limited health literacy, or due to limited access to testing services or even because they do not want to know (e.g., due to stigma, criminalization)¹⁷⁸. Nevertheless, documented seronegativity is a preliminary *must* for PrEP initiation and continuation of use. Public health authorities will need to work hard on preventing and managing misuse of HIV PrEP (e.g., monitoring of HIV status while on PrEP, indications/contra-indications, sub-optimal dosing, fraudulent manufacturing/provision of antiretrovirals)¹⁵⁷.

If PrEP works, who could afford it?

Considering the scale of the HIV epidemic, access to PrEP should be promoted for as many eligible seronegative persons as possible. Unfortunately, universal access to antiretrovirals for people living with HIV - who have no other therapeutic option - is still far from being achieved, especially in resource-limited countries, where those drugs are most needed². Will HIV oral PrEP advocates have to compete with universal access advocates for donors' limited funds?¹³¹ How will priorities be defined...and who will define them?

Beyond the cost of antiretroviral pills for PrEP, expenditures for surveillance and healthcare logistics for optimal benefits might be prohibitive (e.g., enhanced testing services, resistance testing), especially for weak economies with poor healthcare systems. PrEP-related costs would add up very quickly. Although some

modeling studies have predicted cost-effectiveness^{68, 85, 179}, it is not guaranteed that industrialized countries will be able to afford this in the current state of the global economy; let alone resource-limited nations. Modeling cost-effectiveness based on the money saved by infection prevented is informative but comparing PrEP to enhanced behavioural prevention programs (like the ones used as co-interventions during trials) would be at least as helpful for decision-makers. Those issues are profound and need to be discussed further.

Finally, if PrEP cannot be supported by public funds, then individuals who want it may have to pay for it out of their own pocket. Even if private insurance companies decide to cover HIV PrEP costs, it will certainly come with extra conditions, since the client will be “at higher risk”. This would inevitably lead to unequal access and the communities who will have contributed the most to research progress (in developing countries) will predictably be last to benefit from HIV PrEP.

7.2. DISCUSSION ON OBJECTIVE 2: METHODS IN PREP TRIALS

Among the 16 HIV oral PrEP trials identified, 15 were designed as randomized trials, and 2/3 had quality scores of at least 3 over 5, as measured by the Jadad scale. Summary information on designs is usually reported in trial registries, in protocols and in reports. This suggests that most PrEP trials are of high quality and have the potential to yield robust data. However, it is important to remember that while randomization is best to control for known and unknown confounders across study groups, it does not guarantee that the sample selected is *representative* of the target population. It is well known that individuals who consent to participate in research studies are somewhat different from those who opt not to⁸⁶ (self-selection). In the case of HIV oral PrEP, being able to find high-risk though seronegative candidates may suggest that those eligible participants have been using efficient preventative strategies before the trial, may have particular compliance profiles, or may be more naïve, due to recent adoption of risky behaviour. This will impact the effectiveness of PrEP interventions tested as well as the generalizability of the study results. Still, advanced ongoing studies (phases II/III and III) should be adequately powered to provide data with a strong level of evidence, for short-term and longer-term PrEP regimens.

All studies analyzed report the systematic assessment of some measures of physical/ physiological safety, in HIV oral PrEP trials. Outcome measures are presented in protocols and, in less detail, in trial registry files; and investigators frequently use standard grading scales for adverse events. Safety monitoring is always important in clinical trials. In the case of HIV oral PrEP, antiretrovirals are to be used on a regular basis, in *healthy* persons. However, background antiretroviral safety data essentially comes from studies involving HIV *infected* persons taking a *combination* of antiretrovirals - usually compared to some other antiretroviral multitherapy -. Although relatively safe, pills tested for HIV oral PrEP do have known serious side effects. Nevirapine may cause severe rash and potentially lethal liver toxicity¹⁸⁰. Tenofovir and emtricitabine/tenofovir may cause severe kidney toxicity, hepatitis “flare-up” upon drug cessation, potentially lethal lactic acidosis with enlarged liver (especially in women), reduced bone density, and changes in body fat (e.g., “buffalo hump”)¹⁸¹.¹⁸². Limited safety data for tenofovir alone and for emtricitabine+tenofovir bithérapie come from small short-term phase I studies and from one phase II PrEP trial on female adults followed over 12 months (Peterson's trial)¹²³. However, the common use of standard grading scales for adverse events will facilitate pooling of new safety data and comparisons across trials. It is very important that sufficient robust evidence be gathered on antiretroviral therapy in HIV seronegative persons in order to confirm the long-term tolerability of PrEP drug candidates, and also to enhance the adherence of study participants.

In fact, adherence is to be monitored, to some extent, in all 15 studies analyzed for methods.

Information on outcome measures was retrieved in protocols and reports, and sometimes, in less detail, in trial registry files. A common concern with HIV oral PrEP is that, in real life, healthy persons may not be highly compliant to daily chemoprophylaxis, for an extended period of time. An intermittent regimen may be more likely to be adhered to (e.g., pill intake only before an expected risky exposure). Only one small phase I/II trial, so far, is testing intermittent PrEP, or iPrEP^{87, 120}. Based on Peterson's background data¹²³, chances are that this study will show that intermittent PrEP is at least as safe as daily PrEP. But some stakeholders have expressed reservations about the timing of such trials, as we do not know yet whether daily PrEP actually works. How useful would it be to know that patients on iPrEP are more adherent and have good safety outcomes, if ongoing daily PrEP trials yield negative results on efficacy?¹⁸³ In any case, adjusted analyses factoring in adherence data in large daily PrEP studies will be valuable in determining an optimal level of compliance to maximize PrEP efficacy, if it works.

Thirteen of the 16 HIV PrEP trials identified are phase II to III clinical studies, as labeled in trial registries, protocols and/or reports. As a rule, a new pharmaceutical product not previously tested in humans (Investigational New Drug, or IND) must go through a series of increasingly powered studies before being approved for marketing. Phase I studies (20-80 subjects) mark the first time an experimental drug is tested in humans and assess safe dosage range and side effects. Phase II studies assess safety on larger groups (100-300 subjects) as well as effectiveness (the extent to which the drug yields the clinical outcomes expected). Phase III trials enrol more subjects (1,000-3,000) to confirm effectiveness and further characterize the drug's safety profile¹⁸⁴. The definitions of those phases vary^{185, 186} (e.g., some PrEP studies labelled as phase II do not test effectiveness), and phases may overlap within the same study (e.g., phase II/III studies) (Table 6). In the USA, the *Code of Federal Regulations* (chapter 21, paragraph 3.12) defines drug approval requirements¹⁸⁶. It is not clear whether drugs need to strictly go through the 3 study phases, if they have previously been approved for other indications. The USA Food and Drug Administration (FDA) states that "[a] *physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.*"¹⁸⁷ This applies to PrEP since previously approved therapeutic antiretrovirals are being tested for prevention. It is the responsibility of the manufacturer to file an IND for a new indication of its product, and approval may be based on studies conducted outside of the USA (Kimberly Struble, personal email communication, 24 February 2010). This being said, it is only in 2009 that a phase I PrEP randomized trial (Anton's study) was launched, and it does not, actually, focus on oral PrEP, but on the microbicide approach. It is possible that, because previously approved products have already been through phase I trials, it is not required that they go through that phase again (safe dosage range in healthy subjects is already known). In reviewing IND applications, the FDA focuses on safety, for phase I studies, while it also includes an assessment of *scientific quality*, for phases II and III trials¹⁸⁶. In fact, traditionally, it is acceptable for phase I studies not to have a comparison group. Hence, most often, phase II INDs are granted on the basis of safety

data from uncontrolled studies done in humans. However, sometimes, advanced clinical trials fail to confirm results of studies from an earlier phase. As a consequence, investigators may need to go back to the phase I stage or even to pre-clinical research, to figure out what went wrong¹⁸⁸. This might even be the end of the development process for an experimental product. For instance, after a phase II/IIb trial suggested that the topical microbicide PRO2000 might reduce HIV primary infection (30% reduced risk, no statistical significance), there were great hopes that the phase III MDP301 trial would confirm that trend. Unfortunately, it did not¹⁶². HIV PrEP research has already suffered from methodological challenges that led to premature study sites closures, some years ago. And recently, it was announced that one of the six ongoing PrEP efficacy/effectiveness trials would not be able to yield conclusive data on effectiveness, “*given much lower than anticipated HIV incidence in the study population*”¹⁸⁹. The issue of low HIV seroconversion incidence had already been noted in Peterson’s report (phase II trial, partially closed early), back in 2007, though¹²³. Maybe HIV PrEP research has moved forward too quickly and would benefit from more robust early phase studies to properly evaluate the feasibility and value of more advanced trials.

Three antiretroviral regimens have been tested for HIV oral PrEP: nevirapine, tenofovir, and emtricitabine/tenofovir. Although nevirapine is seldom cited in PrEP-related articles, my systematic review identified one report of a phase I/II trial that tested this drug. Nevirapine (NVP, Viramune®) has been quickly left out as a PrEP candidate, though, possibly due to less favourable safety and resistance profiles^{85, 190}. The emtricitabine/tenofovir combination (FTC/TDF, Truvada®) now tends to be favoured over tenofovir alone (TDF, Viread®), based on animal data suggesting a higher efficacy^{65, 191}. However, tenofovir in monotherapy continues to be tested as it has been argued that “[s]imilar to the strategy for tuberculosis, the number of drugs needed for HIV chemoprophylaxis may be less than that needed for effective treatment”¹⁹². Although HIV oral PrEP protocol teams consistently justified the choice of their test-drug(s), few defended their selection over other antiretrovirals. It has been proposed that other antiretrovirals would be valid candidates as well, though. Derdelinckx *et al.* listed criteria to consider in choosing test-drugs for HIV oral PrEP: safety profile, ease of use, mode of action and pharmacology, and cost-effectiveness⁸⁵. They concluded that tenofovir and emtricitabine were good options, but that lamivudine (3TC, Epivir®) was theoretically the most promising. Also, after a recent pharmacological study, raltegravir is being considered for future PrEP clinical trials¹⁹³. And a “*long lasting formulation*” of rilpivirine, an experimental antiretroviral, is to be tested as *intra-muscular* PrEP (monthly injections: www.clinicaltrials.gov/ct2/show/NCT01049932). I found very few papers relaying that discussion on the best PrEP drug candidate(s). It is possible that tenofovir and emtricitabine/tenofovir benefit from a stronger lobby than other antiretrovirals for the PrEP research, which could delay research efforts focusing on more promising products.

Considering safety, on the one hand, standards for the prevention of sexual transmission seem quite

consistently provided to PrEP study participants (at least risk-reduction counselling), although behavioural co-intervention features vary across trials. Details on the standard of prevention provided in PrEP trials are given in protocols and consent forms, and sometimes, in less detail, in trial registry files and reports. A straightforward way to test antiretrovirals for PrEP would be to compare PrEP alone versus a placebo. Although this can be done in animal research, it would be totally unacceptable in humans. This is because there is an efficacious and well-established standard of prevention. And in such situations, it is unethical to conduct placebo-controlled studies since it deprives participants from an intervention that would insure best protection¹⁹⁴. Not providing the standard of prevention would make participation too risky since HIV infection may lead to severe morbidity, chronic disability, and even death. PrEP investigators worked around this issue by providing the standard of HIV prevention to all participants, with half of them receiving the test-drug and the other half receiving a comparator. This is a key feature of PrEP trials that might cause confusion if not clearly acknowledged: PrEP trials actually test a complex prevention intervention (*antiretroviral + behavioural prevention*). This will have important repercussions on the interpretation of the trials' results and on their practical application.

On the other hand, measures for preventing blood-borne transmission in PrEP trials appear to be sub-optimal. Among the 15 studies that focused on HIV sexual transmission, 8 did not explicitly exclude injecting drug users. None of these eight teams reported provision of co-intervention specific to blood-borne exposure, although one team gave some justification for that. As for the one trial focusing on injecting drug users, its protocol says that study staff was to provide *bleach* to allow *re-use* of injection equipment as well as *methadone* for the treatment of addiction. But the United Nations agencies currently support programs that include: 1) drug abuse treatment (especially methadone maintenance), 2) outreach activities, and 3) syringe and needle exchange¹⁹⁵. The PrEP protocol team argued that “[c]onsistent with Thailand's HIV prevention policy, drug injection equipment was not provided or exchanged at participating clinics”, and that “sterile syringes and needles are readily available without prescription at pharmacies for 8 Thai baht (about US\$0.20)”¹³⁴. Uninvolved investigators have further explained that possession of syringes is occasionally used as evidence for drug-related offence by Thai authorities. Hence, providing syringes to study participants would put them at risk of getting into trouble with the police⁷³. Nonetheless, others have counter-argued that the Thai government had actually been working on implementing a harm-reduction program for drug users and that the issue was rather that “the United States government, who sponsors the trial, bans federally funded organisations (including the Centers for Disease Control and Prevention, who are overseeing the trial) from supporting needle and syringe exchange”¹⁹⁶. Past strategies of the Thai government had “highs and lows”¹⁹⁷ and politics may directly impact the conduct of clinical research. However, the Declaration of Helsinki¹⁹⁴ states that:

“The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.” (Declaration of Helsinki, 2000, paragraph 29); and that:

“No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration” (Declaration of Helsinki, 2000, paragraph 9).

Based on these guidelines, this trial's protocol should have been amended but I found no evidence for this. This study has been active since 2005 and results are expected to be released in 2010.

Only two study teams cited references supporting the effectiveness of their behavioural co-intervention. Those studies' protocols mentioned a previous randomized trial that had been *“tailored to the [local] context”* and to specific issues related to the study population. The other protocol teams did not justify the characteristics of their behavioural co-interventions and did not discuss them in relation with prevention programmes locally available. This is a serious consideration for the generalizability of HIV oral PrEP trials' results. For instance, if the behavioural interventions used as co-interventions are not sustainable in communities hosting the trials, this may complicate PrEP roll-out efforts post-trial and affect effectiveness.

It is also worth noting that social adverse events were considered, to some extent, in nine of the 15 PrEP studies analyzed. Based on the protocols reviewed, social outcome measures have been neither consistently nor systematically collected in PrEP trials, though. Participation in a PrEP trial may affect social life in many ways. For instance, relational issues may occur between a participant and his/her partner, family, neighbours or work colleagues. This might be due to the stigma attached to HIV (or to the fact of being involved in something related to HIV), due to HIV seroconversion disclosure, or due to the demands of study participation (e.g., extended hours away from home for testing purposes). PrEP trials have received much public attention, which has not always been positive. In Cameroon, for example, rumours and suspicion from the general population accelerated the closure of the study site¹⁹⁸. PrEP investigators would benefit from identifying and closely monitoring social outcomes or “surrogate measures” that might predict the occurrence of social harm that would negatively affect trial participants and the trial itself. One way of doing this could be, with the input of psychosocial experts, to actively collect information on social incidents and to systematically assess their relatedness with trial participation.

Another important aspect of PrEP research is that trials' timelines overlap. Based on start dates and end dates provided in registry files and in reports, some studies are to finish before others. If their results are conclusively negative, this might mean that further research would be futile. And this might mean that ongoing studies might be terminated early. Moreover, PrEP research is conducted in parallel with other fields of biomedical HIV prevention research. For instance, if new results of a microbicide trial clearly demonstrate the

efficacy of a topical agent, this will change the current standards of HIV prevention. And it would make the conduct of ongoing trials even more challenging, as they would need to be reassessed for feasibility, relevance and appropriateness. Indeed, participants should then receive the new best standard, which will further reduce HIV seroconversion rates and the chance to demonstrate PrEP efficacy.

HIV detection algorithms are usually clearly presented in protocols, although some descriptions were not detailed enough to assess their adequacy. In the absence of a valid surrogate outcome for HIV infection, seroconversion - or evidence of no seroconversion - is the single best outcome for assessing efficacy, in HIV prevention trials¹⁵. It is also important in the assessment of safety. So, it is important that HIV status be adequately measured before, during and after the intervention period. It is unclear why eight of the fifteen protocol teams analyzed for methods chose to use more than one algorithm, within the same trial. Only one of them provided some justification by mentioning costs considerations in relation to HIV testing equipment. Furthermore, testing algorithms have seldom been validated in host community before the trial. This might affect the internal validity of a prevention trial. Indeed, the algorithm may not be appropriate for a particular setting, and HIV tests predictive values heavily depend on HIV prevalence in the target population⁹¹.

In addition, only seven PrEP teams planned on preserving participants' samples in order to test them retrospectively for HIV antigens, hence taking into account the "window period", based on protocols reviewed. It usually takes 2 to 8 weeks (25 days, on average) for HIV antibodies to be detectable after an infectious exposure¹⁹⁹. Seroconversions occurring soon after intervention initiation - as most endpoints in Peterson's trial¹²³ - or soon after the last antiretroviral dose taken may lead to bias. Indeed, the infectious exposure may actually happen shortly before enrolment. And it is biologically plausible that HIV oral PrEP might delay the infection or might temporarily suppress viral load¹⁴³. Therefore, if only antibody tests are used, it increases the risk of enrolling participants who are in primo-infection phase but were screened as seronegative. These participants may develop resistance to the test-drug and end up with limited treatment options for their HIV infection. In addition, if such participants are not identified by further testing (e.g., retrospective HIV antigen testing) and are included in the analyses, conclusions drawn on PrEP efficacy may be very wrong. This kind of bias may have serious consequences and needs to be prevented, considering that only few seroconversions are expected to occur, even in large prevention trials. More recent and larger trials tend to take this into consideration, though, which would reduce the risk of bias at a meta-analysis level.

If PrEP research yields positive results, how will it impact public health?

As pointed out above, all PrEP trials have actually been testing *complex* interventions, that is, antiretroviral pill(s) *combined with* a behavioural prevention regimen. This is to address the ethical requirement to provide the highest standard of care available, in order to minimize risks for study participants³⁵. But stakeholders are still wondering *how good would be good enough* for PrEP efficacy to warrant roll-out. Would a 60% risk difference between intervention and control groups be acceptable? What about 30%? What about 15%?

One may argue that any statistically significant positive result (i.e., relatively less seroconverters in intervention group) would demonstrate that PrEP has an “added value” and thus would be better than nothing. Indeed, some people who have access to behavioral prevention tools chose not to adhere to them; and some people do not use such resources because they don’t have access to them, they are not aware of them, or they are not health-literate enough. If prophylactic pills are recommended instead of the “ABC” behavioral approach, how will PrEP be presented to beneficiaries so they understand that they still *can* get infected?

Although some stakeholders have advocated for early PrEP implementation planning²⁰⁰, this will most certainly represent a challenge, especially in resource-limited countries. Indeed, although poorer countries bear most of HIV/AIDS burden and provide the bulk of PrEP study participants, they also struggle to provide basic primary care to their populations. Health systems in richer nations also have their limitations and many first-line workers there are not well informed about HIV PrEP research. Roll-out plans will need to consider the capacities of local healthcare workforce, health system structure and infrastructures, political leadership, as well as economic factors and community preparedness.

If PrEP research yields negative or null results, could PrEP research still be beneficial?

It is likely that if PrEP alone works, it will not be 100% efficacious. The addition of behavioural prevention in PrEP intervention serves also to enhance prophylaxis. Now, if PrEP trials’ results are negative for efficacy but positive for behavioural safety, it will likely be due to co-interventions (we already know that the “ABC” works). In many resource-limited communities, access to prevention programmes is limited or inexistent. Improving current access would be a clear benefit for host communities. Reduced risk-taking behaviors during a study would suggest that participants can gain knowledge and/or confidence they may not have gotten outside of a HIV prevention trial. In Ghana, for instance (Peterson’s trial)¹²³, reported use of condoms increased and number of new partners decreased, on average¹⁵³. And in Thailand, frequency of drug injection and needle sharing markedly decreased²⁰¹. Such evidence could and should be used to support implementation of stronger behavioral prevention programs in host communities.

7.3. DISCUSSION ON OBJECTIVE 3: ETHICS APPRAISAL OF PREP TRIALS

ETHICS CONSIDERATIONS REPORTING, AT THE STUDY LEVEL

Based on the ethics analysis framework designed for this review, 56% of the checklist items were found in reviewed documents, on average, in the 14 studies ethically appraised (58%, after excluding outliers). Variations across studies were noted in the overall reporting quality of ethics considerations, and in the reporting quality of all 8 ethical principles explored. Not surprisingly, more information could be extracted for studies that had more documents available. However, variations remained, even when analyses were restricted to those trials. This suggests that the reporting quality of ethics considerations could be much improved, and that the level of consideration for ethical issues is not homogeneous across HIV PrEP studies.

Ethics scores did not appear to correlate with standard quality scores. In other words, higher Jadad scores did not always correspond to more ethics considerations reported. The Jadad scale is a validated, commonly used tool that gives information on the robustness of a study's methods. The discrepancies between Jadad scores and ethics scores illustrate that ethical considerations in PrEP research goes beyond designing a randomized double-blind trial and reporting all withdrawals. Interestingly, all four studies closed prematurely (due to ethics/methods concerns) had a Jadad score of 3 or more. So, what may look like a well-designed study may not become a successful one, if relevant ethical issues are not addressed.

In general, more ethics considerations (58% of checklist items) were found for studies with 3-4 target documents available, compared to studies with only 1-2 document(s) available (6% of items). This was observed for overall reporting of ethics considerations and for each ethics principle. Besides, none of the studies with 1-2 document(s) reviewed had a protocol or a consent form available. This suggests that protocols and consent forms should be considered key source documents in the ethics analysis of HIV PrEP research.

On average, more ethics considerations were reported for PrEP efficacy/effectiveness trials than for trials focusing on other primary questions, at study level (61% of checklist items versus 43%). After excluding studies with no protocol/consent form available, it is in this sub-group analysis that the largest differences were observed, in general and for six ethics principles. The 2 exceptions were *favorable risk-benefit ratio* and *independent review* (biggest differences were seen in sub-group analysis based on study site). So, in reporting ethics considerations, focusing or not focusing on efficacy/effectiveness appeared, generally, to make a bigger difference than either the involvement of a USA site or an antecedent of early

closure. For instance, on average, non efficacy/effectiveness documents mentioned 30% ethics items for *collaborative partnership*, 8% ethics items for *social value*, and 42% ethics items for *fair selection of study population* whereas efficacy/effectiveness documents mentioned, on average, 50%, 57% and 83% of checklist items for those principles, respectively. This higher level of reporting ethics considerations might simply be because there is more at stake in efficacy/effectiveness trials. Those trials are more publicized, as they focus on the question “*Does PrEP work?*”, which remains central to PrEP research. And their results are awaited with very high expectations, which puts more pressure on the investigators.

Similarly, more ethics considerations were reported for studies conducted outside of the USA, compared to studies with at least one USA site, even when outliers were removed (63% versus 48% of checklist items). It is in this sub-group analysis that the biggest differences in median sub-scores were observed, for *favorable risk-benefit ratio* (75% versus 50%, favoring trials with no USA sites) and *independent review* (55% versus 70%, favoring trials with at least one USA site). This finding about the *independent review* principle might reflect limitations in institutions regulating clinical research, in developing countries. Otherwise, trials with no USA site had a higher median ethics score and higher median ethics sub-scores. It is unclear why ethics considerations were less reported for studies with participants from the USA. It might be that efficacy/effectiveness trials tended to report more ethics considerations, and only one efficacy trial involves the USA. Another *tentative* explanation would be that past controversies related essentially to participants in developing countries and subsequent ethics guidelines focused on resource-limited communities. PrEP has not caused public debate in Northern America as it has in Asia and Africa. So, trials conducted in a richer country *may* be perceived as less likely to trigger ethical concerns. Thus ethical considerations *may* be addressed in less detail by PrEP protocol teams.

Finally, more ethics considerations were reported for studies partially or fully closed prematurely, compared to studies with no antecedent of premature closure, when outliers were removed (65% versus 58% of checklist items). Hence, some ongoing trials had ethics scores lower than some halted trials. These results are based on an ethics appraisal that assessed PrEP studies in a systematic way, using criteria common to all trials. Such results were unexpected since ethics and methods concerns were clearly reported as leading reasons for early site closures, in 4 PrEP trials. **Moreover, trials closed early had higher ethics sub-scores than trials not closed early**, except for *scientific validity* (52% versus 62%) and *independent review* (50% versus 60%). These findings suggest that 1) reporting many ethics considerations in a protocol may not guarantee that a study will be *perceived* as ethical; 2) gaps in *scientific validity* and *independent review* may have been core issues in halted trials; 3) there is a persistent need to promote and enforce ethics guidelines developed for biomedical HIV prevention trials.

ETHICS CONSIDERATIONS REPORTING, AT THE PRINCIPLE LEVEL

Principle 1: collaborative partnership

Ethics considerations pertaining to *collaborative partnership* were among the least reported with, on average, 48% of the checklist items found in documents reviewed (50%, after excluding outliers).

Most research teams appear to have local collaborators (*checklist item 1.1.2*), including community advisory groups (*item 1.2.5*), who actively contribute to HIV oral PrEP projects. All 14 HIV PrEP trials appraised were sponsored by American institutions and all but 2 involved at least one developing country. It is encouraging that study initiators work in collaboration with scientists and non scientists based in host communities. This can indeed create a sense of common ownership, and make the trials more acceptable and more beneficial to both parties.

However, for less than half studies appraised did we find evidence about locals contributing to designing the research question (*item 1.2.2*), consultations with locals regarding local sustainability of interventions or sustainability of site after trial completion (*items 1.2.6 and 1.2.7*), standard ethics training given to research staff (*item 1.3.1*), research literacy programs offered to locals (*item 1.4.1*), or investment in host country human capacity and physical infrastructures (*item 1.4.2*). All those factors, if not considered, may hinder the suitability and sustainability of trials' benefits to the host community. For instance, Page-Shafer *et al.* did have agreements with the Cambodian government. They also reported efforts to inform the host community about their trial and making contact with community organizations, through public meetings, formative research, focus groups, and key informants interviews. Still, "*not all those who engaged with [them] felt a genuine sense of involvement*"¹²². Eventually, ethics-related concerns were publicly raised and at the end, the Cambodian Prime Minister had the trial cancelled²⁰². In Peterson's trial, proper authorizations had been granted by local regulatory authorities at multiple levels²⁰³. The study sponsor had previously been active for over a decade in Cameroon, conducting community projects²⁰⁴; and local scientists were actively involved in the trial¹²³. Nevertheless, when a French television channel broadcast a report suggesting that the trial was unethical²⁰⁵, it triggered growing public concerns⁷¹. The same government that had authorized the study, based on a review of its protocol²⁰³, ended up auditing then suspending it²⁰³. Durable partnerships require shared motivation to initiate, time to develop and mutual efforts to maintain. And not any partnership will do, for a particular project. My findings suggest that despite efforts made in collaborating with locals, in PrEP research, more emphasis should be put on harmonizing local collaborators' standards and needs with the scientific aims and methodological requirements of clinical trials.

Principle 2: social value

Ethics considerations pertaining to **social value** were the least reported with, on average, 31% of the checklist items found in documents reviewed; this remained true after excluding outliers (43%). This domain is highly relevant to ethical concerns that have been reported, regarding early PrEP trials, and have been focused on in recent guidelines^{1, 97}. Emanuel *et al.* postulated that “*the social value of research for the host community must be explicitly specified and enhanced*” so that “*generation of knowledge (...) lead to improvements in health*”⁹². Such considerations were somewhat embedded in traditional pillars of bioethics (e.g., beneficence, justice)⁴⁵. But the internationalization of biomedical research and a raised awareness about global equity gaps have probably contributed to increased considerations for the social implications of clinical research and to novel interpretations of traditional ethics principles⁴⁴.

For less than half studies appraised did we find information about the social context in host community (**checklist item 2.2.2**), a local knowledge translation plan (**item 2.3.1**), or a discussion on the potential impact of the PrEP study on local healthcare system (**item 2.4.1**). This suggests that there may not be clear expected benefits for most communities contributing to HIV oral PrEP research (beneficence pillar)⁴⁵. Based on the history of clinical research and on the commercial drive inherent to the pharmaceutical industry²⁰⁶, one may suspect that if PrEP is proven valuable, it will tend neither to be intensely promoted nor to be implemented in resource-limited countries, at least not without constraints or delays.

It is worth noting that 8 study teams reported plans to facilitate access to PrEP drug after trial completion (**item 2.3.3**), in case of positive results. These plans were not very detailed in protocols but they were typically about providing drug for free or at-cost to all study participants for a pre-determined period of time (e.g., one year). In fact, since 2003, Gilead Sciences Inc. offers “*substantial price reductions through [its] Access Program in more than 125 countries, representing (...) the regions hardest hit by the AIDS epidemic.*”²⁰⁷ This program was created for *therapeutic* needs, i.e., for persons living with HIV. Some protocol teams have mentioned, however, that arrangements had been/were being negotiated with Gilead so antiretrovirals *for prevention* be made available through that program, if PrEP works. Pharmaceutical companies are key stakeholders and their involvement is most desirable in research efforts to control the epidemic. However, there have been some concerns expressed about the functionality of Gilead's Access Program. In the past, agents from Médecins Sans Frontières [Doctors Without Borders] declared serious administrative challenges that caused long delays and made it difficult for physicians in eligible resource-limited countries to obtain the drugs²⁰⁸. An access program is a nice idea but time will tell if it actually works.

Principle 3: scientific validity

Ethics considerations pertaining to *scientific validity* were more or less reported with, on average, 55% of the checklist items found in documents reviewed (58%, after excluding outliers).

For more than half studies did we find information about general methodological features, e.g., study rationale (*items 3.2.1, 3.2.5*), technical feasibility (*item 3.3.3*), analytic plan (*items 3.2.28, 3.2.29*), and independent data review (*item 3.2.15*). Were also found for more than half studies some considerations for HIV clinical management, such as pre- and post-test counselling (*item 3.2.23*), and clinical care plan for seroconverters (*item 3.2.25*). This speaks for the expertise of HIV oral PrEP investigators in basic clinical trials methodologies. However, the appropriateness of the methods may be weakened if not contextualized.

For instance, for less than half studies appraised did we find information about social and political factors in host community (*item 3.1.1*) or the involvement of behavioural and social scientists in early planning stages of trial (*item 3.3.2*), despite frequent mentions of pre-trial research conducted in host community (*item 3.3.1*). Political and social characteristics of the host community may influence feasibility of a trial, as well as the way a trial is conducted, the interpretability of the results, the external validity of results, and the extent of local benefits during and after trial¹. HIV is inherently related to sex, blood and death, all of which are still taboos in many cultures. Since it arose, the epidemic has been fuelled by stigma and thus, it has had tight links with psychosocial factors, both at the individual and at the community levels. So, behavioural and social experts can be key collaborators on a PrEP trial¹⁵. For instance, they can help promote culturally viable relationships between scientists and the host community and contribute to define, monitor and interpret relevant behavioural and social outcomes. For instance, demonstration of effectiveness or even acceptability of PrEP may require tangible benefits not only for participants but also for their partners, their families and their community. Experts in psychosocial sciences are essential for the planning, design and success of research in a transcultural context. More involvement of such specialists is much needed in PrEP research.

In addition, for less than half studies appraised did we find information on a plan for basic care such as clinical referral for candidates screened out (*item 3.2.24*), comprehensive perinatal care for participants who would become *pregnant* (*item 3.2.26*), or HIV testing and care of participants' partners (*item 3.2.21*). Clinical research should not be taken for clinical care and investigators need to make that clear for recruited participants and for themselves, to prevent confusion and false expectations (sometimes termed "*therapeutic misconception*")⁵². However, the tenth paragraph of the Declaration of Helsinki states: "*It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject*"¹⁹⁴. It has been argued that this responsibility should apply throughout the research process. Research process includes clinical and laboratory investigations in order to ascertain eligibility of recruited participants,

monitor safety, and minimize risk for participants and their community. Inevitably, there will be exclusions based on screening and withdrawals based on monitoring results. Individuals who are screened out or withdrawn from the intervention should be guaranteed access to adequate care, as appropriate. If clinical investigators are not to provide that care themselves, they should at least have mechanisms to facilitate referrals to accessible and affordable services in the host community¹.

On a more technical note, for only 5 or less studies appraised did we find a mention of multiple sources being used to estimate seroconversions rate during trial (item 3.2.2), a justification for the study visits schedule (item 3.2.11), or an evidence-based futility stopping rule (item 3.2.19). As underlined in the *Institute of Medicine* (IOM)'s report, estimating HIV seroconversion incidence *a priori*, for HIV prevention trials, is both crucial and challenging¹⁵. PrEP trials' participants are recruited based on the fact that they belong to populations at higher risk (due to their personal characteristics, to their life style or to HIV prevalence in their community). It is very difficult to accurately assess the risk at baseline (usually self-reported) and to predict to what extent exposure will be maintained throughout a HIV prevention trial. If a slower than expected HIV seroconversion rate occurs during a study, this may mean that no clear difference will be observed between intervention group and control group - this happened in Peterson's trial¹²³ and is happening in Thigpen's trial⁻¹⁸⁹. Although HIV seroconversion rate can also be used as an indicator for safety, this is particularly important for trialists conducting efficacy/effectiveness studies. To prevent methodological failures, it is essential to factor in data/assumptions from diverse sources²⁰⁹ (e.g., incidence rates from similar studies, expected effect of behavioural co-interventions), and to adjust predictions based on epidemiological data on incidence (e.g., rate documented for target population).

Nevertheless, the events-driven approach, for seroconversion rates, is becoming more common (item 3.2.27) in efficacy trials, based on protocols reviewed. This could help reach the number of endpoints needed to establish whether PrEP prevents HIV or not. But this may require extending study duration or increasing sample size which, in turn, will incur further costs, in a context of global economic constraints¹³¹, and further delays, while the public has been building up high expectations, in regards to PrEP research²¹⁰.

A concerning finding, though, is that for only 6 studies appraised did we find clear information on quality control measures in the promotion of behavioural prevention during PrEP trial (item 3.2.9). Quality control measures reported in protocols included specific Standard Operating Procedures and specification of key information to be routinely given during counselling. A key question about HIV oral PrEP trials has been about the quality of the counselling provided to participants⁷². Indeed, one recurrent and legitimate concern is that investigators - especially those conducting efficacy trials - may face one particularly serious conflict of interest. Indeed, they have to provide the standard of HIV prevention to study participants and, in the same time, they need a sufficient number of endpoints to occur so as to avoid futility. And the

Declaration of Helsinki (paragraph 5) states that “*considerations related to the well-being of the human subject should take precedence over the interests of science and society*”¹⁹⁴. It is important that PrEP investigators demonstrate that they address this important consideration. And local authorities should not only demand that clear strategies be planned for but also monitor the implementation of those measures throughout the trials.

Although most study teams reported the contribution of a DSMB/DMC (Data Safety Monitoring Board/Data Monitoring Committee: *item 3.2.15*), for less than half studies did we find evidence that such a group would include at least 33% local members (*item 3.2.16*) or would have the option of unblinding to insure participants’ protection (*item 3.2.17*). DSMBs are groups of experts not involved in a study that periodically review data of ongoing trials. Their role is to monitor safety outcome as well as other methodological indicators (e.g., enrolment rate, endpoint occurrence rate). Based on data reviews, DSMBs make recommendations to the research team about the relevance of continuing or discontinuing the study. This oversight may lead to the early termination of a trial if there is sufficient evidence for excessive harm, striking efficacy, or obvious futility⁸⁶. Hence, DSMBs are to protect the best interests of participants. The Institute of Medicine recommended that local experts be represented on DSMBs so as to take into account cultural considerations, during data review¹⁵. Like for local ethics review boards, the competence of DSMBs contributing to PrEP research might need to be strengthened and locals may need to be more empowered in the process of independent data review.

Principle 4: fair selection of study population

Ethics considerations pertaining to the *fair selection of study population* were among the most reported with, on average, 67% of the checklist items found in documents reviewed (with or without outliers).

In general, populations studied were well justified for the stated trials' objectives (*item 4.1.1*), and efforts are reportedly made to minimize the risks of participating in the studies, based on social factors (*item 4.3.2*). It is important that target population be scientifically justified, based on the study question (principle of *justice*)⁴⁵. And participating individuals and communities should not be overly exposed to risk, even if they are at risk anyway, outside of a trial's context (principle of *non-maleficence*)⁴⁵.

Conversely, a comprehensive discussion on the generalizability of results (*item 4.1.2*) was found for only 5 studies appraised. PrEP investigators consistently mention considerations for target viral type in the target population and/or the target HIV transmission mode. But little is reported about the target health system(s). The ultimate goal of clinical trials is to apply experimental results in real-life settings so as to improve population health. The majority of the communities hosting PrEP trials should, ideally, be given priority as beneficiaries, since they are in the regions of the world with highest HIV prevalence. But many of them are also among the poorest nations. The World Health Organization Knowledge Management and Sharing (KMS) group proposed a definition for *knowledge translation* in lower and middle income countries: the "*synthesis, exchange and application of knowledge by relevant stakeholders to accelerate the benefits of global and local innovation in strengthening health systems and improving people's health*". However, Tugwell *et al.* estimated that "*uptake and use of [innovative] interventions among the poorest populations is at least 50% less than among the richest populations (...)*"²¹¹. If it is proven that PrEP is an acceptable, safe and efficacious intervention for the prevention of HIV infection, it would be important to design and test inventive knowledge translation mechanisms applicable to identified beneficiaries in developing countries.

Principle 5: favorable risk-benefit ratio

Ethics considerations pertaining to *favourable risk-benefit ratio* were among the most reported with, on average, 63% of the checklist items found in documents reviewed (75%, after excluding outliers, tied with *Principle 7: informed consent*).

For more than half studies appraised did we find a clear discussion on the risks versus the benefits of the PrEP study (*item 5.2.1*). For the other studies, risks and/or benefits were usually listed but without a discussion balancing the pros and cons of the research project. This is a fundamental requirement, in a protocol: "*Reviewers should not allow research to begin unless the potential benefits of the experimental intervention outweigh the risks to participating individuals and groups.*"¹.

Similarly, for more than half studies appraised did we find a clear mention of some plan to follow-up on mother and/or child's outcomes should female participants become pregnant during the trial (*items 5.1.2 and 5.1.3*). Unlike nevirapine¹⁸⁰, tenofovir and emtricitabine/tenofovir are not recommended in pregnant and breastfeeding women. Animal studies have suggested they may be harmful but evidence in humans is lacking. So, as a precaution, 10 of 12 PrEP study teams enrolling women opted to withdraw participants should they get pregnant during the follow-up period. Still, as per the Institute of Medicine's recommendations, most PrEP teams reported plans to monitor safety outcomes in pregnant women and their fetuses/infants. And some PrEP teams also mentioned reporting data to the *Antiretroviral Pregnancy Registry* (www.apregistry.com). This could provide important new data on the safety of tenofovir and emtricitabine/tenofovir in those populations.

Only 2 study teams clearly reported data on the burden of a particular clade - targeted by study - in the host country(ies) (*item 5.1.1*)¹, although the type of HIV targeted (1 and/or 2) was consistently indicated for all PrEP trials appraised. HIV of type 1 is the most common world-wide, especially its sub-type C, whereas its sub-type B is the most common in industrialized countries. But there are many viral strains, and their prevalence vary with geographic regions²⁵. If a trial is designed for a clade that is not significantly prevalent in the host community, this could hinder its internal validity, and it may not benefit recruited participants. However, specificity at the level of the viral sub-type might not be as critical for pre-exposure chemoprophylaxis as it is for HIV vaccine research since drugs tested are known to have a wide spectrum of efficacy across most common viral clades (www.gilead.com). Nevertheless, "*fewer data are available on the genetic mechanisms of drug resistance in non-B viruses, and some in vitro and in vivo observations suggest that the various subtypes may respond differently to certain antiretroviral drugs*"²¹². Still, limited reported considerations for this item might not be a major issue, since most PrEP protocol teams focusing on efficacy report plans to test resistance.

Principle 6: independent review

Ethics considerations pertaining to *independent review* were more or less reported with, on average, 50% of the checklist items found in documents reviewed (60%, after excluding outliers).

For only 6 or less studies appraised did we find information about bioethics laws or regulations in force in host country(ies) (*checklist item 6.1.1*), or on bioethics guidelines developed in host country (*item 6.2.3*). And 12 study teams mentioned some bioethics guidelines among which none had been conceived in a developing country. Because ethics considerations are influenced by culture, ethics guidelines must be relevant to the place where they are to be applied. And to insure that guidelines will be followed, they can be enforced through legally binding regulations³⁹. Industrialized countries commonly have locally designed guidelines and laws to regulate clinical research activities, but there are “*great disparities between and within countries*” in the developing world²¹³. Using American bioethics guidelines could be totally irrelevant in other countries (at least in some aspects) and even international guidelines must be adjusted to local situations. Where there is no appropriate capacity to oversee clinical research, there is more risk of exploitation for study participants. The adequacy of conducting a trial in such conditions should be questioned.

In the same vein, none of the documents reviewed reported measures to ensure independence and competence of ethics review committees (*checklist item 6.3.1*) or to prevent conflicts of interest during ethics review (*checklist item 6.3.2*). When found in source documents, information on ethics committees was generally limited to the mention of a review process, the committee name and/or its coordinates. This was not enough to assess competence and independence. So, it is not possible to exclude probable issues like inadequate scientific review or improper assessment of the social impact of trial on host community. About the early closure of the Cameroon PrEP study site¹²³, Ngnié-Téta *et al.* noted that the review process was very likely flawed. At that time, the *Comité National d’Éthique*, or CNE [National Ethics Committee], was under the authority of the Ministry of Health, with “*no financial autonomy, (...) no subsidy, and no office to do its job. Moreover, until the [tenofovir] affair, the committee was not keeping any reliable file archiving system for ongoing trials conducted in Cameroon.*” [free translation]²¹⁴. An investigation conducted by African academia on several African countries’ CNEs suggested that such problems are specific neither to PrEP nor to Cameroon²¹⁵. Other reviews found that ethics committees in developing countries tend to have issues with training their members, defining their mandate, forming the committees, getting funds, and accessing reference texts²¹³. Again, if there is no competent local authority to review PrEP protocols, trial participants will not be adequately protected from faulty procedures. The need for and modalities of capacity-building and sustainable capacity strengthening should always be considered, in transnational research.

Principle 7: informed consent

Ethics considerations pertaining to *informed consent* were among the most reported with, on average, **58% of the checklist items found in documents reviewed** (75%, after excluding outliers, tied with *Principle 5: favourable risk-benefit ratio*).

For more than half studies appraised did we find a clear mention of an iterative consent process (*item 7.4.1*). In most PrEP trials appraised, consent was sought at least twice during the study (e.g., upon screening, upon enrolling, before HIV testing). UNAIDS experts considered it important that “[r]esearchers and research staff should take efforts to ensure throughout the trial that participants continue to understand and to participate freely as the trial progresses.” This is to give repeated opportunities to re-consider participation in the trial, in accordance with the principle of *autonomy*⁴⁵.

Yet, for only 7 studies appraised did we find planned strategies to prevent/address coercion (*item 7.5.1*). Investigators who did address this in their protocols used terms such as “coercion”, “coercive”, “coerced”, or “undue inducement”. Strategies to prevent or address coercion included research literacy training, facilitated access to independent information sources, and sanctions for study staff who would exert coercion on a study participant. Coercion is the act, process or power of restraining or dominating by force (www.merriam-webster.com). So, it is fundamentally opposed to the concept of voluntary participation, which is promoted in modern bioethics guidance documents. Coercion may be plain and obvious, or it can be subtle and unrecognized unless disclosed by the person that perceives it as such. Furthermore, what is identified as coercion may be culture-dependent. David Appelbaum has noted that “[p]opulations in developing countries are often thought to be subject to a variety of coercive influences, ranging from pressures exerted by authority figures to difficulty understanding that research participation is voluntary”²¹⁶. For instance, participants in the Bangkok TDF study reportedly described “feelings of ‘Kreng jai,’ or ‘not disturbing others’ activities,’ rendering them unable to refuse a request, especially when it is made by (...) someone higher in the social hierarchy”²¹⁷. Such cultural perspectives clearly hinder the value of the “consent” given. Although coercion is, in general, hard to measure, there are some guidelines to prevent situations of coercion¹. More emphasis should be put on preventing and addressing coercion in HIV PrEP trials and psychosocial experts could, here again, be valuable contributing experts.

Nonetheless, more than half study teams reported considerations given to cultural sensitivities (*item 7.2.3*) - including language preference (*item 7.2.1*) -, to the use of plain language in documents given to participants (*item 7.2.2*), to illiteracy (*item 7.4.3*), to the provision of oral explanations (*item 7.4.4*) and to systematic measures to assess comprehension of prospects/participants (*item 7.4.5*). These are all

positive strategies to enhance the consent process, especially in resource-limited communities where comprehension may be more challenging due to lower education level and low socio-economic status¹. It is a good thing that PrEP investigators are taking sociocultural factors into consideration as part of their consent process; these factors are key in the obtention of a true informed consent from study participants.

Despite these valuable efforts, only 4 study teams discussed the relevance or irrelevance of supplementary community or familial consent (item 7.3.1). Parental consent was discussed in two PrEP studies recruiting participants under the local age of consent; and partner's consent is required in both PrEP studies focusing on serodiscordant couples. The UNAIDS guidelines say that "[i]n some communities, it is customary to require the authorization of a third party, such as a community elder or head of a family, in order for investigators to enter the community or to approach individuals" ¹. Depending on the community, such authorization might be required *before* approaching certain sub-groups (e.g., women, adolescents), or before approaching the community as a whole. Planning for and proceeding with the proper approach demands a deep knowledge of the target community's customs and values. For this, the early involvement of psycho-social experts familiar with the target community would be crucial. Failure to involve culturally appropriate third parties in the consent process could indeed lead to slow recruitment, to social harms (e.g., domestic violence, stigmatization) during the trial, or to excessive drop-out rates.

Similarly, only one study team clearly mentioned that some time could be allowed to read consent form off-site before signing (item 7.4.2). The other protocols required that consent form be read, discussed and signed at the study site. The UNAIDS guidelines simply recommend that "[t]ime should be allowed to consider participation, discuss with others such as partners, and ask questions."¹ I think that, in some cultures, it might be intimidating for prospects to decline consent when they do not fully understand the study plan. This might create a situation of coercion. Giving prospects opportunities to discuss the consent form content with someone they know and trust, outside of a study clinic and before they consent, could make the consent more free and more informed, make the trial more acceptable at the community level, minimize social harmful effects (e.g., rumours), and improve compliance. The external person consulted could be a family member or a knowledgeable authority figure (e.g., an acquaintance with a higher education). I think it would be a plus to offer this option to prospect participants, for the enhancement of the consent process, in PrEP clinical trials.

Also, only 3 study teams reportedly discussed community consultations for determining appropriate compensation (item 7.1.1). When this was reported, investigators mentioned initiatives like involving community members (e.g., Community Advisory Board) in the elaboration of consent forms or discussions with local partners to determine appropriate compensation based on local life conditions. The distinction may be blurry between undue inducement and fair compensation or even with "benefits". For instance, provision of free regular testing - needed to monitor safety - may constitute inducement if participants cannot access or afford

such medical follow-up outside of a trial²⁰⁵. The UNAIDS guidance states that “[e]xtraneous benefits, such as payment or ancillary services, such as HIV risk-reduction interventions or reproductive health care services, should not be considered in the risk-benefit analysis.”¹ Insights from locals (scientists and non-scientist) are essential in defining what type and amount of compensation would be adequate, and their contribution to PrEP studies should include this kind of advisory role.

Finally, enrolment consent forms in HIV PrEP research are almost 5,000 words, on average (the equivalent of about 10 pages). The Microsoft word count function was used to compute text lengths. As explained in the *Methods* (section 5.8), I decided not to use Microsoft “readability statistics” (e.g., Flesch-Kincaid Grade Level), as I found they were not culturally appropriate for the systematic assessment of the consent forms for international trials. I did notice, though, that some consent forms were much easier to read than others (e.g., very little jargon, wide line spacing). Three study teams even included pictures or small tables, or used bolding or colors to emphasize key information. It is important that prospects be given all necessary details so they can make an informed decision. However, text length is known to hinder comprehension⁵³. It is encouraging that a majority of PrEP study teams have considered giving the opportunity to discuss prospects’ question orally (*item 7.4.4*) as well as using systematic measures to assess comprehension (e.g., questionnaire: *item 7.4.5*). This suggests that concrete efforts are being made to insure that enrolled participants clearly understand the implications of the study. It would be very informative to further analyze PrEP consent forms for quality. But in any case, efforts should be made to reduce the length of the text to make them less daunting and favor comprehensibility.

Principle 8: respect for recruited participants and study community

Ethics considerations pertaining to the ***respect for recruited participants and study community*** were more or less reported with, on average, 56% of the checklist items found in documents reviewed (56%, after excluding outliers). This was the most stable result in both primary and sub-group analyses: neither the primary study focus nor the study host country nor early closure seemed to influence the extent to which these ethics considerations were reported.

For more than half studies appraised did we find a clear mention of measures to insure participants' confidentiality (*item 8.1.1*), to inform participants of their right to withdraw at any time (*item 8.2.1*), to insure provision of medical care for adverse events during the trial (*item 8.4.2*), and to share study results with the participants and/or the community (*item 8.5.1*). Most protocols reviewed included all of those important considerations. These are not specific to HIV PrEP research and they can be found in generic ethics guidelines^{33, 35, 43}. Still, they were all included in the UNAIDS guidelines for biomedical HIV prevention trials¹. They represent basic human rights (privacy, autonomy)³⁶, responsibilities of medical professionals who conduct research (care for the patient more than for science)³⁵, and intellectual transparency (disclosure of study results)³⁵. Here again, these findings suggest that most PrEP investigators make efforts to respect universal values.

However, only for 5 study appraised did we find information on local health care standards (*item 8.4.1*). Those five protocols mentioned details about HIV treatment standards or prevention services available in the local community. In other protocols, the generic term "*local standard of care*" was sometimes used, without further description. Rarely was the "local standard of care" compared to the standard of care in practice in the sponsoring country or to internationally recommended standards. Now, should the "standard of care" used in trials be: 1) the best available in the world; 2) the standard used in the sponsoring country; or 3) the usual care available in local community? This debate is neither new nor specific to HIV oral PrEP^{76, 218}. Based on my review, it is difficult to assess whether the conduct of PrEP trials is fair for non-participants who may not have comparable access to health care (e.g., free HIV-related counseling, free condoms, free treatment of sexually transmitted diseases).

Also, for only 6 studies appraised did we find information on a plan to update participants with relevant new information (*item 8.3.1*). Although protocol teams commonly report informing participants of their personal test results, it is less frequent to find discussion on more general relevant information. Such information could be results from other HIV biomedical prevention studies and may relate to safety or lead to the establishment of new standards of prevention. This may very well affect the design (e.g., new best standard of prevention to be offered to all participants) or even the relevance of a trial (futility). But it could also

affect the willingness of the participants to remain involved. PrEP investigators should look into developing and sharing mechanisms to update study participants on relevant progress in HIV prevention research. This would give them a chance to decide what would be best for them. A way to avoid conflicts of interest at the investigator level could be to have some independent organization or person who could provide information and advice to participants.

But my review indicates that only one study team mentioned a partnership with an organization that could independently inform and advise study participants (*ethics item 8.4.3*). The UNAIDS guidelines suggest to consider the appointment of an independent party to “*intervene on behalf of participants with outside parties, if necessary and requested*” or to provide counseling “*in order to prevent any real or perceived conflict of interest*”¹. In developing countries, where most PrEP study participants are recruited, medical information and medical services are not as readily available as in industrialized nations (in general). So, the availability of independent advocates would be both valuable and empowering for study participants and their communities.

Moreover, only five study teams reported planned compensatory measures for trial-related harm (*item 8.4.4*). Measures cited usually included extended medical care provided for free by the study team. This number is surprisingly low. Indeed, the US National Bioethics Advisory Commission recommends that “*The U.S. government should not sponsor or conduct clinical trials that do not, at a minimum, provide (...) adequate care of and compensation to participants for injuries directly sustained during research*” (recommendation 1.1b)⁴¹. This is a pretty clear statement from the country sponsoring most of PrEP research. If this recommendation is not addressed in so many approved protocols, does it mean that should harm happen, study participants could be left to their fate? Would it even be made public? A legal analysis of this issue would be useful, and practical implications would depend on local regulatory capacities (e.g., capacity to do audits, authority to demand reparation), which may be lacking in most communities hosting PrEP trials.

Does PrEP research abide with general ethics guidance?

Protocol teams that cited some reference to an ethics document named the *Declaration of Helsinki* and/or the *International Conference on Harmonization's Guideline for Good Clinical Practice*. These general ethics guidance documents are both relevant to HIV oral PrEP. But, as noted above, they are not always respected in some PrEP trials, even in some ongoing trials. Ethics guidelines more specific to HIV PrEP were not cited at all in documents reviewed. However, some PrEP investigators have been involved in the development of both the UNAIDS's guidelines¹ and the IOM's document¹⁵. Yet, like other guidance documents, it can take some time before they are adopted, and they only provide non-binding recommendations. Still, it would make sense that regulators and other decision-makers take the initiative to incorporate those important guidelines into local laws, in order to make them count, both in richer and in poorer countries, for the benefit of study participants.

Were halted PrEP trials “worse” than other PrEP trials?

Based on my review, PrEP trials that got closed prematurely had, on average, more ethics considerations documented in their protocols, compared to other PrEP trials (65% of ethics checklist items versus 58%). And at the principle level, the protocol teams of halted trials reported more ethics considerations for all but two principles: *Principle 3: scientific validity* (52% for trials halted versus 62% for trials not halted) and *Principle 6: informed consent* (50% for trials halted versus 60% for trials not halted). This might mean that scientific methods and informed consent should be given special consideration in HIV oral PrEP research, to make it more ethical. However, those early closures may have had other causes or may simply have been a sign of the times.

Indeed, controversies all started with the mobilization of advocacy groups that feared that human rights of study participants might be violated. In summary, there were 1) a situation of potential abuse of vulnerable groups by powerful institutions 2) popular forces to mobilize the public opinion 3) HIV as a central piece. These elements were put forward in media stories that did not fail to alarm a large audience, both locally and internationally. The storm that began in Cambodia snowballed in Africa. Although some reporters presented some evidence to support their arguments (e.g., copies of study documents), others did not and simply played the sensationalism card. If there had not been any strong advocacy group for Cambodian sex workers initially, to stand for sex workers' rights and go public about their concerns, there might not have ever been so much ado about PrEP research ethics. After all, hundreds of HIV prevention studies are conducted in resource-limited communities, and who knows if they are all ethically conducted?

Do more recent PrEP study documents suggest lessons learned from early studies cancellations?

In spite of variations in ethics considerations across the 8 principles, ethics scores and sub-scores, as well as quality scores tend to improve with ascending data sources dates, for most principles. This suggests that ethics considerations tend to be better reported in more recent study documents. UNAIDS has been promoting the use of its guidelines (e.g., *18th Annual Canadian Conference on HIV/AIDS Research, April 2009*; *5th International AIDS Conference, July 2009*), and is to follow-up on the uptake thereof²¹⁹. But this review does not allow to comment on the potential influence of those specific guidance documents on that tendency. It could simply be a secular trend related to a “practice effect” on the part of investigators, stricter requirements from regulatory agencies, or increased social pressure from community-based advocates.

What did scientists from developing countries write about HIV oral PrEP?

I found only one paper reporting an African viewpoint on HIV oral PrEP research. It was published by Mpho Selemogo, from Botswana²²⁰. The author, although not against PrEP, underlined the relationship between socio-economic factors and ethical perspectives, in HIV prevention research. He also discussed key questions, such as: “*How can we justify testing one of the more [sic] expensive HIV interventions in an area where people do not have access to even the cheapest and proven modalities?*” and “*Why do we insist on testing a product in a place where its prospects of being used are minimal?*” I did no systematic search for opinions about HIV PrEP written by scientists from developing countries. But they seem scarce. Their absence (or invisibility) in the PrEP debate is unfortunate, as they could play such a central role as advocates.

7.4. DISCUSSION ON OBJECTIVE 4: SYNTHESIS OF EVIDENCE

There is still not enough good evidence to conclude on the safety and on the efficacy of HIV oral PrEP⁷⁷. Another systematic review on HIV antiretroviral PrEP came to the same conclusion⁷⁷. Nevirapine, the first HIV oral PrEP drug tested, was deemed tolerable, at infra-therapeutic doses. However, the risk of bias was high in the one study that reported data¹²¹. And nevirapine has a high potential for serious hepatic adverse events and an unfavourable resistance profile^{85, 132}. HIV oral PrEP using tenofovir appears to be safe, both physiologically¹²³ and from a behavioural¹⁵³ point of view, for a daily regimen, at a therapeutic dose. But this is essentially based on a single trial phase II clinical trial, with a follow-up of 12 months. Acceptability at the community level is unclear, considering that 2 sites out of 3 were closed early, and that risk behaviour changes *“may vary by group and over time”*^{122, 153}. Long-term safety (beyond one year) and effectiveness of tenofovir-based PrEP remain to be demonstrated.

New data should become available soon. Indeed, results from several trials are expected to be released in 2010 (one acceptability trial, four safety trials, and one efficacy trial), based on estimates found in registries. But until data are released, expectations should be kept reasonable ... In December 2009, the study sponsor of a PrEP efficacy trial in Botswana announced that it would not be able to demonstrate whether PrEP works, due to a lower than expected seroconversions rate¹⁸⁹. Moreover, although data release will help answer some questions, it may revive others. For instance, some community advocates have already expressed concerns about *“the quality of the data collected”* in the PrEP efficacy trial in injecting drug users (in Thailand), *“due to problems with recruitment methods, and some information obtained through unethical and controversial circumstances”*²¹⁷. More challenges for HIV oral PrEP research might be ahead...

7.5. CHALLENGES & LIMITATIONS

This thesis work was an attempt to conduct an ethical analysis of HIV oral PrEP trials. Bioethics challenges are multi-faceted in nature and a full, perfect ethical appraisal is virtually impossible. Although much work has been put into developing robust methods and efforts were made to faithfully follow the review protocol, the present study does have some limitations.

STUDY DESIGN

This review was not designed to evaluate the quality of the conduct of HIV oral PrEP studies. It mostly assessed the *reporting quality* of study documents: reported study plan (from registry files, protocols and consent forms), and reported actions (from study reports). A quality analysis of HIV PrEP studies would require different approaches, such as a formal audit, a legal investigation, or a field survey. Examining more study documents (e.g., standard operating procedures, clinical trial agreements) and directly observing procedures would obviously require a special permission that is usually reserved to pre-identified authorities (e.g., sponsor or local government). A legal investigation would need to be a case-by-case study, as legal frameworks will depend on the community hosting the PrEP trial. However, it would also identify laws and regulations applicable to American institutions sponsoring international trials. The *NEBRA* report provided some data on local laws and regulations in force in Cameroon, Ghana and Nigeria²¹⁵ and the *International Compilation of Human Research Protections* annually updates a repertory of bioethics laws, regulations and guidelines³⁹. A survey would allow to question involved investigators, collaborators, sponsors, and participants about what the actual conduct is/was like and how it is/was perceived by involved parties. Two documents recently published by the *Global Campaign for Microbicides* were partly based on interviews of community-based stakeholders. They reported the chronology of events that led to study sites closure in Cambodia²⁰² and Cameroon²⁰³. A similar initiative by the *New HIV Vaccines and Microbicides Advocacy Society* yielded a report about what went wrong in Malawi, Nigeria, and Thailand²¹⁷. Those documents are very informative and complement my analysis very well, by offering a community perspective of the ethics of PrEP research.

Only a selected set of source documents were analyzed. More key information might have been found in other types of documents such as local media reports and advertisements. And source documents obtained could have been analyzed in more depth, i.e., strength of evidence presented for justifying the trials; language level in consent forms; side effects as listed in prescribing information against risks listed in consent forms.

Nevertheless, all studies identified were assessed based on the same criteria, which allowed to make comparisons between trials.

INFORMATION SOURCES

I expected that, as PrEP is a novel field, studies would have been registered in at least one major registry, before enrolment start. And, in effect, most PrEP trials are registered, usually before they start. Still, it has been reported that some studies get registered only after completion and that many can get published without being registered²²¹. However, I searched multiple sources in order to maximize the chance to identify all studies. This allowed me to find the report of a non registered completed study (Jackson)¹²¹ and to know about some studies before they got registered (e.g., Hosek, Anton). I could also identify more PrEP trials than any previous review on the topic, and I am confident about the comprehensiveness of my review - as of the time of my last search updates -.

SOURCE DOCUMENTS

My set of documents was incomplete, despite a systematic approach to obtain them. The main reasons were that the documents were inexistent or were not yet finalized. A minority of investigators did not reply to my requests or declined to share their documents, though. I had resource and time constraints for the completion of this thesis. And I was hoping for scientists' collaboration based on good will. So, I decided not to try other routes to obtain missing documents (e.g., direct communication with sponsor, request through the *Freedom of Information Act*). My secondary analysis accounted for those missing data. Still, like An-Wen Chan, I believe that "[t]he time has come to tackle the challenge of making key trial documents public (...) for the sake of patients (...)"²²². This is necessary to enhance transparency and accountability in clinical research.

Also, protocols' outlines are not standardized, which was a challenge for data extraction. For instance, it was common to find outcome measures of interest mentioned outside of the section listing primary, secondary, tertiary/exploratory measures. However, all assessors involved in my review were trained to fully read all sections of the documents' texts, and the accuracy of data extraction was sanctioned by a consensus between independent reviewers. This helped maximize the retrieval of data items that were the basis for the analyses.

Besides, update lags were noted for certain documents (e.g., registry files), and one protocol was not dated, which might have affected the accuracy of the time trends in my analyses (I deduced study chronology based on alternate information sources). Because of the sensitivity of the topic, there was an initial

perception that protocols might not be obtained. So, I decided that I would request the most updated version, as it was felt that investigators would be more comfortable sharing a protocol after one or more amendments. Consequently, some protocol teams had had more opportunities to amend their procedures simply because they had had more practical experience with PrEP trial conduct. This was a factor very difficult to control for, at my level, as HIV PrEP is a fast-moving research field. Between the completion of my analyses and the finalization of my thesis manuscript, five eligible studies had been newly registered (Anton, Hosek, Mutua: www.clinicaltrials.gov) or otherwise publicized (HPTN066 and HPTN067, in planning: www.avac.org). Some other trials had their expected end date changed, and the primary outcome measure of one trial was modified due to futility¹⁸⁹.

Finally, my review did not aim to verify the accuracy of information reported in source documents. My analyses did not take into account extraneous information that might confirm or contradict information used. So, the conclusions I made are essentially based on data extracted from target study-related documents. Throughout my manuscript, I made efforts to insert a wide variety of references that can be consulted by the readers for further information on the many aspects of HIV PrEP ethics. Readers may also refer to my website that presents updates and links about HIV PrEP research (<http://mk-public-domain.yolasite.com>).

ETHICS ANALYSIS FRAMEWORK

Adequacy

Other guidelines could have been the basis of my ethics analysis. However, I believe that those I chose were particularly adequate. UNAIDS's and the IOM's documents are clearly relevant to HIV oral PrEP. And I am aware of one recent ethics analysis based on the 8 principles proposed by Emanuel *et al.*. James Lavery *et al.* used 21 actual studies as cases, to illustrate instances of unethical research, based on each of the 8 principles. Those case studies were from different fields of research, including HIV vaccine research²²³. This suggests that Emanuel *et al.*'s framework is appropriate for the ethics appraisal of HIV oral PrEP research as well. Still, Emanuel *et al.*'s principles might not be the best way to synthesize an ethics analysis, as done in this thesis. For instance, principles proposed are often inter-dependent. So, assigning benchmarks or more specific items to principles was not always straightforward. This may have affected conclusions on the degree of fulfilment of each principle. Also, as suggested by my analyses, scientific validity and informed consent might be more important to consider in PrEP studies. Thus, it might have made more sense to give them more weight in calculating the proportions of ethics considerations reported.

This being said, all but six checklist items were found in at least one of the documents reviewed. And

all those six items are evidence-based, as they were directly derived from UNAIDS's or IOM's guidelines. So, I believe that the set of source documents used for my ethics appraisal were appropriate since a majority of the checklist items were actually found in them. Those items that were not found and those that were infrequently retrieved could serve as a basis to promote better reporting in HIV oral PrEP study documents.

Time effect

My ethics analysis framework is based on the assumption that what is not *acceptable* today should not have been *accepted* in the past. My checklist is based on guidelines developed after some of the HIV oral PrEP trials were initiated or even terminated. Indeed, the first HIV oral PrEP clinical trial was activated before 2003 and three trials were partially or fully closed prematurely in 2004 (Page-Shafer), 2005 (Peterson, Hoffman), and 2007 (Smith). The framework by Emanuel *et al.*⁹² was published in 2004, the guidelines by UNAIDS¹ were released in 2007, and the Institute of Medicine's recommendations¹⁵ were published in 2008. This might have given some advantage to documents developed after those guidelines' release. However, my analytic framework allowed to make comparisons across all trials, based on common standards, and to observe the time trends in reporting ethics considerations. The actual uptake of those guidelines remains to be evaluated and followed up on.

Statistics

The sub-group analyses accounted for only one factor at a time. On top of the availability of a protocol or consent form, I considered three factors that could influence the summary statistics of my quantitative ethics analysis of PrEP trials. These were: the primary question, the host community and antecedent of early site closure. Eight of the 11 studies in the heterogeneity analysis happened to belong to 2 or 3 of those categories. For instance, three of the 11 studies had, in the same time, efficacy/effectiveness as their focus, no site in the USA, and an experience with a premature site closure. These multifactorial influences could not be assessed by my sub-group analysis.

Interpretation

Some ethics items were somewhat subject to interpretation. Bioethics analyses are typically qualitative and, whatever their framework of reference, they are somewhat subjective. The originality of my appraisal is that, to minimize subjectivity, ethics criteria were formulated *a priori* as short statements, mentions about those statements were systematically searched in source documents, and results were summarized quantitatively. In addition, formal standard training of all assessors facilitated familiarity with and use of the ethics checklist, despite an expected learning curve. This gave considerable consistency to the review process.

Scores obtained simply say *how many listed items were identified* in selected source documents, not

whether or not a trial is/was ethical. No “threshold value” was defined as some minimum score that should be considered “ethically acceptable”. So, no such interpretation should be made based on my results. Also, the ethics scores were adjusted based on the assumption that all principles are equal, which, as mentioned in the methods, is arguable, depending on the context or on the assessor’s perspective⁵⁶. Although convenient for results synthesis, proportions of considerations reported may not be a useful statistic outside of a theoretical analysis. From a pragmatic point of view, analyses at the checklist item level might be more relevant. This is why I also reported details on the number of study teams reporting each checklist item ([Table 10](#)).

Generalizability

The validity and the reliability of my ethics checklist were not formally appraised. However, the last seven ethics appraisals were informally assessed for the degree of agreement between assessors. Most disagreements (11 to 26 per conciliation) could be consensually resolved either by examining the reference supporting the decision, or by examining the explanatory note corresponding to the checklist item. Only 3 disagreements were true divergent opinions and required consultation of a third party to be resolved.

It is unclear whether my ethics checklist could be useful to others. Although my checklist can be informative, it might not be convenient for use outside of a theoretical research context. Non validated checklists are used by some research ethics boards as a way to formalize abidance with relevant ethics-related rules and regulations²²⁴. My checklist might be of interest to ethics committee members who may have to review HIV oral PrEP study protocols. Still, this is a very long checklist (101 items, 5 pages). It does take time to become familiar with all the items and to fill it in. This would probably be a hindrance to its acceptability (Dr. David Moher, 23 January 2009, personal face-to-face communication). Again, my checklist is based on the assumption that all the principles and all the items are of equal importance. This might not be the view of local regulators or scientists who may prefer to pick only the items they judge particularly relevant to their local context. Hence, my checklist could be an inventory of ethics indicators that users could be more or less interested to consider, based on their own values and challenges, without necessarily calculating scores.

Furthermore, my ethics checklist was designed for PrEP only, which is limiting. PrEP research could become irrelevant anytime, for instance if other biomedical HIV prevention approaches demonstrate more efficacy, or if PrEP causes harm. Other authors have considered developing checklists for the ethical appraisal of study protocols, with no focus on a particular discipline. In 2005, the ASSERT statement (*A Standard for the Scientific and Ethical Review of Trials*) was proposed as an 18 item-checklist²²⁵. That checklist incorporated the CONSORT statement¹⁰² and some of Emanuel’s requirements to make clinical research ethical⁴⁹. For unclear reasons, the ASSERT initiative was defunct (Dr. Howard Mann, 29 June 2009, personal email communication). The *Equator* group might be more successful with the *Standard Protocol Items for*

Randomized Trials (SPIRIT)²²⁶, which aim to serve the same purpose. With 35 evidence-based items that resulted from a robust validation process, these standards have the potential to be useful in a wide range of disciplines, for the appraisal of study protocols²²⁷.

Hypothetical checklist validation

The final decision about the formulation of the checklist items, their number, and their classification under Emanuel et al.'s principles were essentially based on my personal judgement. Although I did a thorough review of the scientific literature relevant to HIV oral PrEP and I informally obtained input from some local and international experts, I developed my checklist only in the interest of my thesis. I made efforts to retain indicators I perceived as mutually exclusive and most relevant to HIV oral PrEP. But, as per Emanuel et al. noted, "*failing on any one principle (...) makes the research unethical. The proposed benchmarks, however, may not be sufficient and may need revision with experience and time.*"⁵⁶ So, the list of ethics considerations I used for my appraisal, as specifications to the benchmarks proposed, may not be adequate.

I attempted to minimize subjectivity 1) by identifying ethical issues previously reported and discussed in scientific literature and in ethics guidance documents relevant to HIV oral PrEP research, 2) by using these reported issues as criteria for appraisal, 3) by building - *a priori* - a framework that could be used in a systematic way for all HIV oral PrEP trials, 4) by targeting key documents susceptible of containing data items of interest, 5) by providing standard training to assessors for the use of the checklist, and 6) by proceeding with independent reviews sanctioned by a reconciliation process.

Despite those precautions, the methods used to develop an analytic framework could have been more robust. The EQUATOR network has an extensive experience and expertise in developing reporting guidelines and has successfully disseminated several of them (www.equator-network.org). There is no perfect way to develop checklists but the EQUATOR group recently proposed an 18 step-process, focusing on a consensus exercise, for the development of health research reporting guidelines ²²⁸. I outlined in [Appendix 9](#) the process I would follow, ideally, to develop a reporting quality checklist for HIV oral PrEP research.

8.0 CONCLUSION

Is HIV oral PrEP research ethical or not? I have been asked this question over and over, whether I casually discussed my work or formally presented it. This was not quite my research question but this is what many people want to know. A lot has been said about the ethics of PrEP trials, sometimes with heated passion, often based on partial or erroneous information, by both supporters and opponents. My goal was to collect, synthesize and report empirical evidence, in a transparent way, so as to assist others in drawing their own conclusions. **Based on my review, HIV oral PrEP trials' ethics are neither all black nor all white.**

First, my review of PrEP study documents suggests in no way that trials that were terminated early tended to report less ethics considerations than other PrEP trials, although premature closures might have been related to lack of consideration for *scientific validity* and *independent review process*. Second, some lessons from those terminations seem to have been well learned by protocol teams and applied to more recent PrEP studies. However, some critical ethical issues remain disturbingly unaddressed in some protocols of ongoing or planned trials. Unaddressed issues pertain essentially to (social) justice considerations that are neither new to bioethics nor specific to HIV PrEP (e.g., appropriate standard of care, compensation for trial-related harm). Third, I found a lot of variability across trials regarding the extent to which ethical considerations were reported. So, PrEP trials should not all be judged as one. Fourth, study protocols were key source documents for a detailed ethics analysis of the PrEP trials, and I acknowledge the transparency of sponsors who now post their protocols online, and the collaborative spirit of the investigators who kindly shared their documents with me. **Still, assuming that what is on paper is actually being done in the field, how long and how many participants will it take before we know if PrEP (partially) works? At what (cumulative) costs? Will we ever find out?**

Are HIV PrEP research efforts worth it, then? Well, the HIV/AIDS epidemic remains a serious global health issue, and the need for more effective means to prevent the infection remains critical⁶. All well-meaning and conscientious efforts made by any stakeholder deserve to be acknowledged and supported, since everyone would benefit from discoveries leading to a better control of the HIV pandemic. HIV oral PrEP appears to be an interesting concept to investigate and PrEP investigators have taken upon them a great challenge. Still, some have argued that more should be done to insure access to established standard of care (behavioural prevention) before investing in newer less cost-efficient prevention approaches like PrEP. **Determining benefits and harms of HIV oral PrEP will certainly generate important new knowledge. Nonetheless, it remains crucial to insure a high quality of the trials, both scientifically and ethically, including evidence-informed justification for those trials.**

Thus, more efforts should be made, globally, to enforce ethics and methods guidelines relevant to HIV oral PrEP. It is an unfortunate fact that ethics guidance documents have usually been developed “*in response to specific events and to avoid future scandals*”⁴⁹. One would hope that collective experience would prevent history from repeating itself. Still, it took a few public-led early closures of HIV oral PrEP trials to develop suitable ethics guidelines. Now that those guidelines are available, it is unclear to what extent they are being integrated into national policies and laws, enforced by regulators, uptaken by funding agencies, used by investigators, disseminated to AIDS serving organizations and study participants, or considered by editors of scientific journals. These guidance documents resulted from global consensual efforts to improve the acceptability of HIV prevention research at the community level and to prevent methodological failures. It is important that those recommendations be put into practice. I did observe that some investigators do report considerations for those recommendations, in their protocols. **However, it would be safer, for study participants and to help prevent new controversies, to have those guidelines integrated into legally binding international regulations.**

Oral PrEP is important in the landscape of HIV biomedical prevention research. It went through difficult debuts marked by highly publicized community-led premature closures. However, this field seems to currently benefit from a more positive interest from the public and from an ever-increasing support from funding institutions. There have been a rising number of trials and over 20,000 persons are to contribute data. But, for now, we only have limited evidence that tenofovir PrEP is safe to use as a daily regimen. However, the expectations are high and some view PrEP as the next potentially available new tool for biomedical HIV prevention^{200, 229}.

Despite the great pressure they are under, involved stakeholders should be prudent in formulating research updates and comments about PrEP and about its potential, so as to manage unreasonable expectations.

The wait for further evidence on HIV PrEP could soon come to an end, though. Whether results are positive, null or negative, scientific and non-scientific stakeholders need to be prepared to react. Indeed, they will have to decide whether they will implement or recommend changes of behaviours/practice. Although some countries have initiated discussions and planning focusing on PrEP, at the national level (e.g., USA²²⁹, Australia²³⁰, Canada²³¹), many front-liners (e.g., clinicians, community workers) seem to have a limited knowledge, if any, about HIV oral PrEP research. **It is urgent that all stakeholders be sensitized to both the potential and the challenges related to the HIV PrEP approach, and that they get actively involved in public discussions to assess the social value of PrEP in their own communities.**

Such public discussions should be conducted in a collaborative spirit and should be informed by verified facts and information. Although too much information may cause confusion, information sharing is essential to foster a climate of trust, which, in turn, is essential to the progress of clinical research¹²² and to the success of any

subsequent public health initiative. Web-based information technologies can be a useful tool in that regard. The many blogs that have been discussing PrEP matters are rarely backed up by solid references, which leads to misinformation. However, there are high-quality resources and networks open to the public that post, discuss and circulate updates about HIV PrEP research (e.g., www.avac.org). And HIV PrEP is more and more discussed publicly, both in local HIV prevention meetings and in major international HIV conferences. **In addition to those valuable initiatives, it would be beneficial, for transparency, to make all approved study protocols available to the general public.**

Of course, the “general public” includes the communities hosting the trials. More efforts should be made, at the planning stage, to involve locals in the formulation of the research question (for relevance) and in the protocol development (for acceptability). Such interactions would be opportunities for research literacy training and for open discussions around cultural considerations. Consensus should be sought before initiating the trials, considering the best interest of all involved parties, and especially the interest of the potential participants and host community. Ways to facilitate this could be, for the investigators, to become more familiar with participative research approaches, and for the sponsors, to be more flexible with their approval/amendment processes. Locals should also be more empowered to monitor the actual conduct of trials. Along with any relevant operational issues, results should always be published if data were collected - whether they are positive, null, negative or incomplete -. This is to inform future research but it is also a matter of respect for the scientific and non scientific contributors, and of transparency vis-à-vis the community at large. **This kind of measures would help develop and maintain trust in scientific research and would add to the social value of HIV PrEP studies.**

Reflecting on suspicion and mistrust in HIV and international research ethics, John Killen wrote: *“That this ethical controversy has persisted for so long suggests that answers cannot be derived solely from either the fundamental principles of research ethics or in the abundance of existing guidelines and frameworks. One must hope that creative attempts to apply the HIV/AIDS partnership paradigm to this global health research issue might bring about movement toward solutions that help identify research that is important and fair to the communities concerned, and has impact on the broadest possible global scale.”* ⁴⁴. I will echo this author by concluding that, all in all, mutual trust is key - in HIV oral PrEP, as in any kind of clinical research^{122, 222, 232} - at least at three levels. Consumers of scientific literature tend to trust what is reported in published articles, regulatory bodies have to trust investigators based on study documents submitted and, most importantly, clinical investigators need to obtain and maintain trust from host communities and participants. **Transparency and open dialogue throughout all steps of research projects and between all stakeholders should be promoted as the ultimate ethics “principles”.**

9.0 DISSEMINATION

The protocol of this review was shared upon request with key informants. It was not registered, as none of the *Cochrane Collaboration* groups identified and contacted could accept the topic, based on their criteria. However, it is freely available upon request. The concept of this systematic review was presented in plenary at the *First Panafrikan Bioethics Congress*, held in Yaoundé (Cameroon) in May 2008²³³. The analytic description of the HIV oral PrEP trials was presented as a poster at the *18th Annual Canadian Conference on HIV/AIDS Research*, held in Vancouver (British Columbia, Canada) in April 2009²³⁴. Selected arguments in favour of HIV oral PrEP research and the concerns about it were discussed as an oral presentation at the annual meeting of the *Association Francophone pour le Savoir (ACFAS)*, held in Ottawa (Ontario, Canada) in May 2009²³⁵. The methods for the development of the *PrEP Ethics 101* checklist were presented as an electronic poster at the *5th International AIDS Society Meeting*, held in Cape Town (South Africa) in July 2009²³⁶. Selected results of this thesis work were presented orally, in plenary, at the *Annual Review Meeting* of the *University of Nairobi STD/AIDS Collaborative Group*, held in Nairobi (Kenya) in January 2010²³⁷. Two internal presentations were given at the *Ottawa Health Research Institute* in January 2009 and in May 2009. Copies of public presentations were shared with HIV oral PrEP investigators upon request.

10.0 LIST OF ATTACHMENTS

Attachment 1. Reviewer's Brochure

Attachment 2. Data Extraction Form

Attachment 3. PrEP Ethics 101 Checklist

Attachment 4. Consent Content Analysis Form

11.0 TABLES

Table 1. List of studies included in the review (16 studies)

Lead Investigator	Registry	Title (name and/or code)
Jackson	---	<i>A phase I/II study of nevirapine for pre-exposure prophylaxis of HIV-1 transmission in uninfected subjects at high risk (HIV HOP 101, 1 U01 AI054241-01)</i>
Peterson	NCT00122486	<i>Phase 2 Study of Tenofovir Disoproxil Fumarate (TDF) for Prevention of HIV (FHI 9780)</i>
Page-Shafer	NCT00078182	<i>Study of Daily Oral Tenofovir (Tenofovir Disoproxil Fumarate) to Prevent HIV-1 Infection Among Sex Workers in Cambodia (Hope of Women)</i>
Grohskopf	NCT00131677	<i>Phase II Extended Safety Study of Tenofovir Disoproxil Fumarate (TDF) Among HIV-1 Negative Men (CDC-NCHSTP-4323)</i>
Choopanya	NCT00119106	<i>Study of the Safety and Efficacy of Daily Tenofovir to Prevent HIV Infection Among Injection Drug Users in Bangkok, Thailand (CDC-NCHSTP-4370, Bangkok TDF)</i>
Hoffman	NCT00122512	<i>Phase 2a Study of Tenofovir Disoproxil Fumarate (TDF) for Prevention of HIV – An Extended Safety Evaluation (FHI 9876)</i>
Smith	NCT00111150	<i>Study of the Safety and Efficacy of Daily Tenofovir Disoproxil Fumarate for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana (CDC-NCHSTP-4321, BOTUSA MB04)</i>
Thigpen	NCT00448669	<i>Study of the Safety and Efficacy of Daily Oral Antiretroviral Use for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana (CDC-NCHSTP-4940, BOTUSA MB06)</i>
Grant	NCT00458393	<i>Chemoprophylaxis for HIV Prevention in Men (Global iPrEX, 5U01AI06400202, U01 AI064002)</i>
Celum	NCT00557245	<i>Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition Within HIV-1 Discordant Couples (Partners PrEP, 07-7454-A-01)</i>
Hendrix	NCT00592124	<i>Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir (MTN 001, 1-U01-AI068633-01)</i>
Van Damme	NCT00625404	<i>Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Effectiveness and Safety Study to Assess the Role of Truvada® in Preventing HIV Acquisition in Women (FEM-PrEP, FHI 10015)</i>
Chirenje	NCT00705679	<i>Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women (VOICE)</i>
Grosskurth	NCT00931346	<i>A Pilot Study of Pre-Exposure Prophylaxis (PrEP) to Evaluate Safety, Acceptability, and Adherence in at-Risk Populations in Uganda, Africa</i>
Anton	---	<i>A two-site, Phase 1, partially-blinded, placebo-controlled safety, acceptability and pharmacokinetic trial of topical, vaginally-formulated tenofovir 1% gel applied rectally compared with oral 300 mg tenofovir disoproxil fumarate in HIV-1 seronegative adults (IAVI E002)</i>
Hosek	---	<i>Acceptability and Feasibility of a PrEP Trial with YMSM (Adolescent Trial Network PCS082)</i>

Table 2. Reported reasons for premature closures (4 studies)

Trial	Site closed early	Reported reason for early closure
Page-Shafer	Cambodia (Phnom Pen) 13 August 2004	- "stopped before enrolment"; "controversy stemming from local and international activist groups' ethical concerns about standards of health care for volunteers during and after the trial" ¹⁴⁸
Peterson	Nigeria (Ibadan) 7 March 2005	- "date of permanent product withdrawal [was] 7 March 2005"; "stopped by trial sponsors due to concerns about local sites' capacity" ¹⁴⁸ - "irregularities in the performance of the laboratory"; "because of repeated noncompliance with the protocol that was not resolved with staff retraining, enrolment was stopped in March 2005, and the site was closed thereafter." ¹²³
	Cameroon (Douala) September 2005	- "stopped after enrolment"; "controversy related to international debate around trial ethics and standard of care which originated with Cambodian trial" ¹⁴⁸ - "date of permanent product withdrawal [was] 4 February 2005"; "the Ministry of Health suspended study drug distribution in February 2005 primarily in response to concerns about the standard of long-term post-trial care that could be guaranteed to seroconverters." ¹²³ - "Participants continued to come to the clinic for off-product laboratory, pregnancy, and HIV testing, and HIV prevention counseling and condom distribution until September 2005, at which time the Cameroon site was closed." ¹²³
Hoffman	Malawi (city?) November 2005	- "stopped November 2005 before enrolling"; "concerns on the part of Malawi Ministry of Health that studies of tenofovir as PrEP could complicate use of the drug as a treatment for HIV-infected individuals" ¹⁴⁸ - "The study (...) was never [sic] approved by the local IRB in Malawi (...)." (Dr. Irving Hoffman, personal email communication, 3 November 2008)
Smith	Botswana (Francistown & Gaborone) March 2007	- "switched from TDF Q1 2007" ¹⁴⁸ - "Because the [Thigpen] trial had originally planned to study tenofovir alone (before there was evidence to support initiating trials of tenofovir plus emtricitabine), the [Smith] study had already enrolled 71 high-risk men and women. Researchers continued to follow these participants until the new trial was initiated to obtain data on the safety of tenofovir alone." ¹⁴⁷

Table 3. HIV oral PrEP trials' host countries (16 studies)

	AFRICA	ASIA	AMERICA
	Botswana	Cambodia	Brazil
	Cameroon	Thailand	Ecuador
	Ghana		Peru
	Kenya		USA
	Malawi		
	Nigeria		
	South Africa		
	Tanzania		
	Uganda		
	Zambia		
	Zimbabwe		
Jackson			•
Peterson	•		
Page-Shafer		•	
Grohskopf			•
Choopanya		•	
Hoffman	•		
Smith	•		
Thigpen	•		
Grant		•	•
Celum	•		•
Hendrix			•
Van Damme	•		
Chirenje	•		
Grosskurth	•		
Anton			•
Hosek (undetermined)			

Table 4. Design features of HIV oral PrEP trials (16 studies)

Lead Investigator	Population	Sample size	# Arms	Design	Test-pill (s)	Comparator(s)
Jackson	mixed* (♂ and ♀)	33	3	controlled cohort	NVP	escalated doses
Peterson	♀ (heterosexual)	936	2	parallel RCT	TDF	placebo
Page-Shafer	♀ (heterosexual)	960**	2	parallel RCT	TDF	placebo
Grohskopf	♂ who have Sex with ♂	400	4	parallel RCT	TDF	placebo; delayed placebo; delayed TDF
Choopanya	injecting drug users (♂ and ♀)	2 400	2	parallel RCT	TDF	placebo
Hoffman	♂ (heterosexual)	400**	2	parallel RCT	TDF	placebo
Smith	♀ and ♂ (heterosexual)	71†	2	parallel RCT	TDF	placebo
Thigpen	♀ and ♂ (heterosexual)	1 200	2	parallel RCT	FTC/TDF	placebo
Grant	♂ who have Sex with ♂	3 000	2	parallel RCT	FTC/TDF	placebo
Celum	serodiscordant couples (heterosexual)	3 900	3	parallel RCT	TDF, FTC/TDF	placebos
Hendrix	♀ (heterosexual)	144	6	crossover RCT	TDF§	"self"
Van Damme	♀ (heterosexual)	3 900	2	parallel RCT	FTC/TDF	placebo
Chirenje	♀ (heterosexual)	4 200	5	parallel RCT	TDF, FTC/TDF§	placebos
Grosskurth	serodiscordant couples (heterosexual)	150	4	parallel RCT	FTC/TDF	placebo; intermittent placebo; intermittent FTC/TDF
Anton	♀ and ♂ (hetero / homosexual)	18	4	multiple sequence RCT	TDF§	"self"
Hosek	♂ who have Sex with ♂	99	3	parallel RCT	FTC/TDF	placebo; no pill

* both sexes, Men who have Sex with Men, injecting drug users or sex partners thereof, sex partners of persons living with HIV

** never enrolled † planned sample size was 1 200 § TDF gel was another active intervention (not eligible for this study)

FTC=emtricitabine TDF=tenofovir NVP=nevirapine

Table 5. Eligibility criteria for HIV exposure (15 studies)

Risk factor	Risk parameter	Population	Age range
Rate of sexual acts	over 1 consensual receptive anal, in previous year	♂, ♀	18 and up
	over 1 vaginal, in previous 3 months	♀	18-40
	over 6, on average, in previous 3 months	♂, ♀	18-65
	over 1 vaginal, in previous 2 weeks	♀	18-35
	over 4 penile-vaginal in previous 4 weeks	♀	18-45
	on average, 3 per week	♀	18-35
Rate of sexual partners	1 or more non exclusive ♂ partner, in previous 12 months	♂	18-60
	"multiple" partners, in previous 12 months	♂, ♀	18 and up
	2 ♀, in previous 3 months	♂	18 and up
	over 1, in previous 3 months	♂, ♀	18-29
	over 1, in previous 3 months	♂, ♀	18-39
	over 4 ♂, in previous 6 months	♂	legal age and up
	over 2 ♂, in previous month	♀	18-35
	over 4 ♂, in previous month	♀	18-35
Unprotected sexual activity	no or inconsistent condom use with single ♂ partner	♂	legal age and up
	"unprotected sex acts"	♂, ♀	18 and up
	with HIV+ partner not on antiretrovirals, in previous 3 months	♂, ♀	18-49
Sexual partnerships	sex with HIV+ person	♂, ♀	18-29
	sex with HIV+ person	♂, ♀	18-39
	be a Man who has Sex with Men, have sex with HIV+ person, or have sex with injecting drug user	♂, ♀	18 and up
Exchange of sex for profit	vaginal/anal sex for material profit, in previous year	♀	18 and up
	sex exchanged for material compensation	♂	legal age and up
Use of injection drugs	injection drug use, in previous 12 months	♂, ♀	20-60
	injection drug use	♂, ♀	18 and up
Sexually transmitted diseases	diagnosed sexually transmitted disease, in previous 6 months	♂	legal age and up

Table 6. Primary questions and phases of studies (16 trials)

Lead Investigator	Phase	Primary question(s)
Jackson	I/II	safety, tolerability, pharmacokinetics
Peterson	II	effectiveness, extended safety
Page-Shafer	II/III	safety, effectiveness
Grohskopf	II	extended safety, tolerability
Choopanya	II/III	efficacy, safety
Hoffman	2a	extended safety, feasibility
Smith	II/III	extended safety, efficacy
Thigpen	III	extended safety, efficacy
Grant	III	efficacy, safety
Celum	III	efficacy, safety
Hendrix	II	adherence, acceptability, pharmacokinetics
Van Damme	III	effectiveness, safety
Chirenje	2b	effectiveness, extended safety
Grosskurth	I/II	safety, tolerability, acceptability, pharmacokinetics, adherence, behavioral
Anton	I	safety
Hosek	"preparedness"	feasibility, acceptability, safety, adherence

Table 7. Main sources of financial or in-kind support (16 studies)

	BMGF	CDC	CONRAD	FHI	Gilead	IAVI	NIH	U of W	USAID
Jackson							x		
Peterson	x			x	x		x		
Page-Shafer	x			x			x		
Grohskopf		x			x				
Choopanya		x			x				
Hoffman				x	x				
Smith		x			x				
Thigpen		x			x				
Grant	x				x		x		
Celum	x				x			x	
Hendrix			x		x		x		
Van Damme	x			x	x				x
Chirenje			x		x		x		
Grosskurth						x			
Anton			x		x		x		
Hosek							x		
	5	4	3	4	12	1	8	1	1

Governmental	CDC	Centres for Disease Control and Prevention	(www.cdc.gov)
	NIH	National Institutes of Health	(www.nih.gov)
	USAID	United States Aid for International Development	(www.usaid.gov)
Non Governmental	BMGF	Bill and Melinda Gates Foundation	(www.gatesfoundation.org)
	FHI	Family Health International	(www.fhi.org)
Academic	CONRAD	CONtraceptive Research & Development program	(www.conrad.org)
Academic-governmental	U of W	University of Washington	(www.washington.edu)
Public-private	IAVI	International AIDS Vaccine Initiative	(www.iavi.org)
Industry	Gilead	Gilead Sciences, Inc.	(www.gilead.com)

Table 8. Follow-up characteristics (15 studies)

Follow-up characteristic	Number of trials
On drug follow-up duration (3 to 48 months)	
< 12 months	4 studies
12 months	4 studies
12 months or more	5 studies
> 12 months	2 studies
Off-drug follow-up (1 to 8 weeks)	12 studies
Care plan for adverse events during follow-up period	13 studies
Namely cited healthcare institution(s) for provision of medical care	5 studies
Information on local healthcare standards	5 studies
Compensation for harm related to study product	5 studies

Table 9. HIV detection features (15 studies)

HIV detection feature	Number of trials
HIV prevalence reported	
<i>At regional level</i>	3 trials
<i>At country level</i>	1 trials
<i>At city/community level</i>	4 trials
<i>(no HIV prevalence reported)</i>	7 trials
HIV detection algorithm justified in local context	
<i>Conform to national strategy</i>	1 trial
<i>Validated in host community</i>	2 trials
<i>(algorithm not justified)</i>	12 trials
HIV detection algorithm	
<i>One algorithm only</i>	6 trials
<i>More than one algorithm</i>	8 trials
<i>(no algorithm reported)</i>	1 trial
HIV laboratory testing	
<i>Rapid test</i>	12 trials
<i>ELISA</i>	10 trials
<i>Western Blot</i>	9 trials
<i>Immunofluorescence assay</i>	1 trial
<i>Greenscreen®</i>	1 trial
<i>(no test namely reported)</i>	1 trial
Considerations for HIV antibody seroconversion window	
<i>RNA or DNA polymerase chain reaction</i>	7 trials
<i>(no antigen detection testing reported)</i>	8 trials

Table 10. Number of trials reporting each ethics checklist item (14 studies)

B # - # = principle number - benchmark number (order as per Emanuel et al.'s framework)⁹²

n = number of trials reporting checklist item

N = number of trials for which checklist item is relevant

* item excluded when appraising trials designed to be conducted in the USA only (irrelevant for 2 studies)

** item excluded when appraising trials not designed to focus on efficacy/effectiveness (item irrelevant for 5 studies)

*** item excluded when appraising trials designed to include men only (item irrelevant for 3 studies)

ITEM #	n	N	PrEP ETHIC 101 ITEM
PRINCIPLE 1: COLLABORATIVE PARTNERSHIP			
B1-1			
1.1.1	0	14	strategy to ensure legitimacy of community partners chosen to represent host community
1.1.2	10	14	mention of partnership with clinicians/scientist(s) and with policy-makers in host country
1.1.3	9	14	mention of creative and flexible partnership with HIV and/or non-HIV networks
1.1.4	4	14	mention of strategy for combining safety information from concurrent trials of similar products
B1-2			
1.2.1	9	14	community network/partners for the study are namely identified and their roles clearly defined
1.2.2	3	14	active contribution of host community in the development of the study question
1.2.3	10	14	active contribution of local partners in trial planning
1.2.4	11	14	active contribution of local partners in trial conduct and monitoring
1.2.5	9	14	mention of a Community Advisory Mechanism (CAM)
1.2.6	2	14	consultation with community/stakeholders regarding sustainability of interventions locally
1.2.7	5	14	consultation with community/stakeholders regarding sustainability of site, after trial completion
B1-3			
1.3.1	2	14	standard ethics training given to research staff in all study sites
1.3.2	1	14	intervention(s) deemed culturally appropriate for use among host community
1.3.3	6	14	strategies to minimize/reduce stigma/discrimination attached to target population

ITEM #	n	N	PrEP ETHIC 101 ITEM
B1-4			
1.4.1 *	3	12	mention of a research literacy program for host community
1.4.2 *	3	12	mention of investment in host country human capacity and physical infrastructure
B1-5			
1.5.1	9	14	benefits for study participants/host community are clearly delineated
B1-6			
1.6.1 *	6	12	intellectual property is shared with investigator(s) based in host country
1.6.2	1	14	some/all data to be owned/co-owned by local institution/organization
1.6.3	1	14	mention of other agreed sharing of reward
PRINCIPLE 2: SOCIAL VALUE			
B2-1			
2.1.1	10	14	identification of the beneficiaries of the research
B2-2			
2.2.1	7	14	documented assessment of HIV burden in host community
2.2.2	4	14	description of social context in host community, as relevant to study conduct
B2-3			
2.3.1	4	14	description of knowledge dissemination plan within host community
2.3.2	1	14	mention of long-term partnership plan with stakeholder(s) based in host community
2.3.3 **	8	9	drug proven safe and effective to be made available and affordable to host community, post trial
B2-4			
2.4.1	4	14	discussion on expected impact of trial on health-care system/services in host community
PRINCIPLE 3: SCIENTIFIC VALIDITY			
B3-1			
3.1.1	4	14	trial design is informed by social and political study(ies) of host community
B3-2			
3.2.1	13	14	references from previous research/scientific arguments justifying conduct of the study
3.2.2 **	5	9	use of triangulation for estimation of HIV incidence rate (sample size determination)

ITEM #	n	N	PrEP ETHIC 101 ITEM
3.2.3	10	14	description of strategies for achieving accrual rate goals and for maximizing retention
3.2.4	10	14	plans for evaluation of effectiveness of recruitment plan
3.2.5	8	14	scientific justification of test-drug(s) choice and intervention regimen(s)
3.2.6	7	14	statement justifying chosen comparator(s)
3.2.7	0	14	use of both blinded and unblinded control groups
3.2.8	0	14	randomized comparisons of behavioural risk-reduction interventions incorporated into design
3.2.9	6	14	quality control measures in the promotion -by research staff- of HIV prevention for participants
3.2.10	0	14	behavioural co-intervention was field tested during planning phase
3.2.11	3	14	scientific justification of study timeline
3.2.12	13	14	strategy to monitor actual degree of exposure of selected participants during trial
3.2.13	14	14	description of monitoring plan for adherence
3.2.14	11	14	safety outcome measures include measures for psychological and/or social harm
3.2.15	10	14	mention of a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)
3.2.16	1	14	at least one-third of DSMB/DMC members are host country community members
3.2.17	6	14	clear statement that DSMB/DMC has the option of unblinding to insure participants' protection
3.2.18	4	14	statement of basis and criteria for recommendation by DSMB/DMC to modify trial's size/duration
3.2.19	5	14	futility stopping rule relies on evidence of a sustained impact on cumulative HIV incidence
3.2.20	8	14	study will allow provision of information on both short and long-term benefits of intervention
3.2.21	3	14	HIV testing and treatment plan for potential participants'/participants' partners
3.2.22	5	14	each HIV testing test is to be consented to and to include pre-test and post-test counselling
3.2.23	11	14	each HIV testing test is to include pre-test and post-test counselling
3.2.24	5	14	description of care plan for potential participants screened HIV positive
3.2.25	12	14	description of care plan for HIV seroconverting participants
3.2.26 ***	2	11	description of complete action plan for participants who become pregnant
3.2.27 **	6	9	"events-driven" approach for the statistical analysis (actual seroconversion cases)
3.2.28 **	9	9	primary analytic strategy is intention-to-treat for efficacy endpoint
3.2.29	14	14	potential impact of adherence is taken into account for statistical analyses

ITEM #	n	N	PrEP ETHIC 101 ITEM
B3-3			
3.3.1	8	14	mention/description of extensive pretrial research in host community
3.3.2	2	14	mention of involvement of behavioural and social scientists in early planning stages
3.3.3	7	14	consultations/strategies to ascertain technical and material feasibility of trial
PRINCIPLE 4: FAIR SELECTION OF STUDY POPULATION			
B4-1			
4.1.1	10	14	scientific justification of study population, in relation to internal validity
4.1.2	5	14	scientific justification of study population, in relation to generalizability of results
B4-2			
4.2.1	8	14	justification of study population, based on risk minimization
4.2.2	10	14	description of educational initiatives to inform host community –at large- about the study
B4-3			
4.3.1	4	14	acknowledgment that study population is vulnerable
4.3.2	9	14	description of measures to minimize risk of exploitation of participants
PRINCIPLE 5: FAVORABLE RISK-BENEFIT RATIO			
B5-1			
5.1.1	2	14	HIV strain(s) targeted by study is/are an important public health problem in host community
5.1.2 ***	8	11	strategy to explore test-drug(s) safety for pregnant women and their foetuses
5.1.3 ***	8	11	participants who become pregnant are followed whether drug is discontinued or not
B5-2			
5.2.1	11	14	statement/discussion about risk-benefit ratio
PRINCIPLE 6: INDEPENDENT REVIEW			
B6-1			
6.1.1	6	14	reference to bioethics laws/regulations in host country or acknowledgement of absence thereof
6.1.2	12	14	reference to protocol review/approval process by ethics committee based in host community
6.1.3	9	14	acknowledgement of the right of regulatory body based in host community to discontinue trial

ITEM #	n	N	PrEP ETHIC 101 ITEM
B6-2			
6.2.1	13	14	trial registered with an international trial registry
6.2.2	14	14	funding source(s)/ in-kind support disclosed
6.2.3	2	14	mentioned reference to/use of bioethics guidelines developed by host country
6.2.4	10	14	mention of international consultation or use of international guidelines
B6-3			
6.3.1	0	14	specification of measures taken to ensure independence and competence of ethics review
6.3.2	0	14	specification of measures taken to prevent situations of conflict(s) of interest
6.3.3	2	14	strategy to assist local ethics committee in reaching international standard procedures
PRINCIPLE 7: INFORMED CONSENT			
B7-1			
7.1.1	3	14	consultation with host community for appropriate recruitment procedures and compensation
7.1.2	11	14	recruitment method is explained and participants source(s) is/are specified
B7-2			
7.2.1 *	10	12	information available to participants/community in local official language(s)/main dialect(s)
7.2.2	10	14	information disclosed in plain language and clearly stating potential risks for study participants
7.2.3	9	14	information disclosed to participants/community in a culturally sensitive manner
B7-3			
7.3.1	4	14	discussion on relevance of supplementary community and familial consent procedures
B7-4			
7.4.1	10	14	informed consent is an iterative process
7.4.2	1	14	time allowed to read consent form off-study site before signing
7.4.3	8	14	specific modalities for conduct and documentation of consent process for illiterate participants
7.4.4	10	14	oral explanations given and opportunities to ask questions offered
7.4.5	10	14	systematic measures to assess comprehension of disclosed information by potential participant
B7-5			
7.5.1	7	14	description of measures to prevent/address coercion

ITEM #	n	N	PrEP ETHIC 101 ITEM
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PRINCIPLE 8: RESPECT FOR RECRUITED PARTICIPANTS AND STUDY COMMUNITY

B8-1

8.1.1	11	14	specification of procedures to protect confidentiality of recruited and enrolled participants
-------	----	----	---

B8-2

8.2.1	11	14	systematic steps to insure that enrolled participants know their rights regarding withdrawing
-------	----	----	---

B8-3

8.3.1	6	14	statement about updating information disclosed to participants with relevant new information
-------	---	----	--

8.3.2	1	14	consent to be confirmed in cases that may affect participant's willingness to remain involved
-------	---	----	---

B8-4

8.4.1	5	14	description of relevant local health care standards in each study site
-------	---	----	--

8.4.2	11	14	description of health monitoring/care plan for study participants during trial period
-------	----	----	---

8.4.3	1	14	discussion about appointing ombudsperson or partnering with independent organization
-------	---	----	--

8.4.4	5	14	compensation plan for trial-related harm
-------	---	----	--

B8-5

8.5.1	8	14	statement about giving feedback to participants/host community about study results
-------	---	----	--

Table 11. Exploring heterogeneity: outliers in ethics appraisal

MEDIAN SCORE		MEDIAN SUB-SCORES							
		collaborative partnership	social value	scientific validity	fair selection of study population	favorable risk-benefit ratio	independent review	informed consent	respect for recruited participants & study community
PRIMARY ANALYSIS									
14 studies appraised	56	48	31	55	67	63	50	58	56
11 studies with protocol/consent form	58	50	43	58	67	75	60	75	56
3 studies without protocol/consent form	6	10	0	17	0	0	30	8	0
SUB-GROUP ANALYSIS									
Efficacy: 9 out of 14 studies	61	50	57	61	83	75	60	83	56
outliers removed: 9 efficacy	61	50	57	61	83	75	60	83	56
outliers removed: 2 non efficacy	43	30	8	41	42	63	60	48	56
No USA site: 10 out of 14 studies	60	50	50	58	75	75	45	67	56
outliers removed: 8 with no USA site	63	50	57	59	83	75	55	79	56
outliers removed: 3 with USA site(s)	48	35	17	48	67	50	70	50	56
Closed early: 4 out of 14 studies	53	35	43	47	58	63	45	67	56
outliers removed: 3 closed early	65	50	57	52	100	75	50	75	56
outliers removed: 8 not closed early	58	50	36	62	67	75	60	71	56

Legend:

least reported, on average

most reported, on average

Table 12. Risk of bias analysis at study level (15 studies)

	YES	NO	UNCLEAR	N/A
COCHRANE COLLABORATION'S TOOL¹⁰⁶				
<i>Allocation sequence adequately generated?</i>	3	1	11	0
<i>Allocation adequately concealed?</i>	9	3	3	0
<i>Knowledge of allocated intervention adequately prevented during study?</i>	8	1	6	0
<i>Incomplete outcome data adequately addressed?</i>	7	7	1	0
<i>Reports of study free of suggestion of selective outcome reporting?</i>	1	0	1	13
<i>Study apparently free of other potential risks of bias?</i>	0	15	0	0
CONSIDERATIONS FOR SELECTION BIAS				
free of risk/suggestion of self-selection?	0	15	0	0
free of risk/suggestion of sub-optimal testing for baseline HIV serostatus?	7	5	3	0
free of risk/suggestion of sub-optimal assessment of baseline HIV exposure?	5	0	10	0
CONSIDERATIONS FOR ASCERTAINMENT BIAS				
free of risk/suggestion of bias in measuring safety outcomes?	10	2	3	0
free of risk/suggestion of bias in measuring efficacy/effectiveness outcomes?	6	5	4	0
free of risk/suggestion of sub-optimal compliance?	11	2	2	0
free of risk/suggestion of sub-optimal adjustments for confounders?	10	1	4	0
free of risk/suggestion of undisclosed competing interests?	0	7	8	0

Table 13. Risk of bias analysis at outcome level (15 studies)

<i>ESTIMATED RISK OF BIAS</i>	Within studies		Across studies
<i>For safety assessment</i>	HIGH	1	LOW
	LOW	10	
	UNCLEAR	4	
	N/A	0	
<i>For efficacy/effectiveness assessment</i>	HIGH	0	LOW
	LOW	8	
	UNCLEAR	1	
	N/A	6	

12.0 FIGURES

Figure 1. Study selection flow diagram

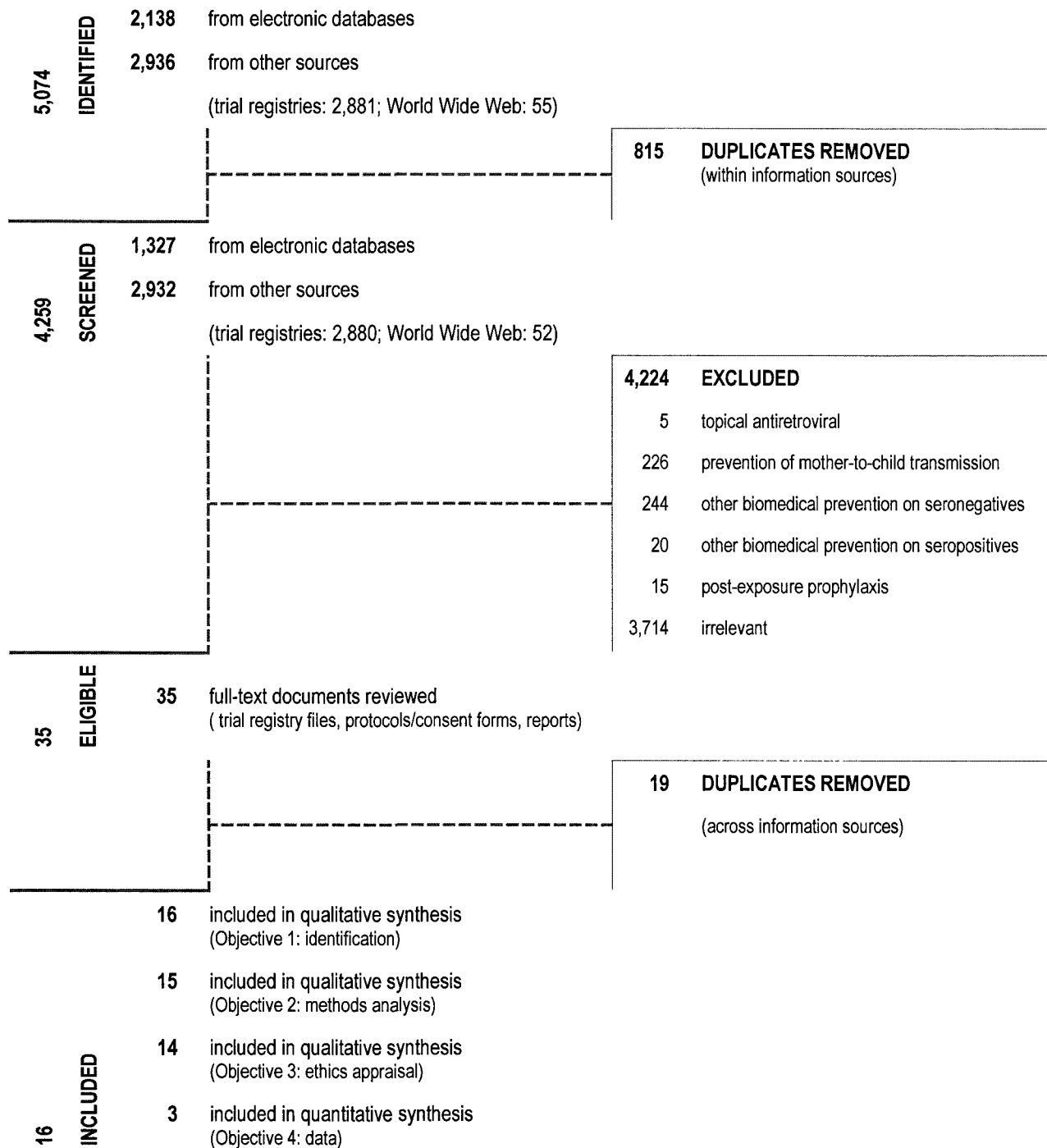
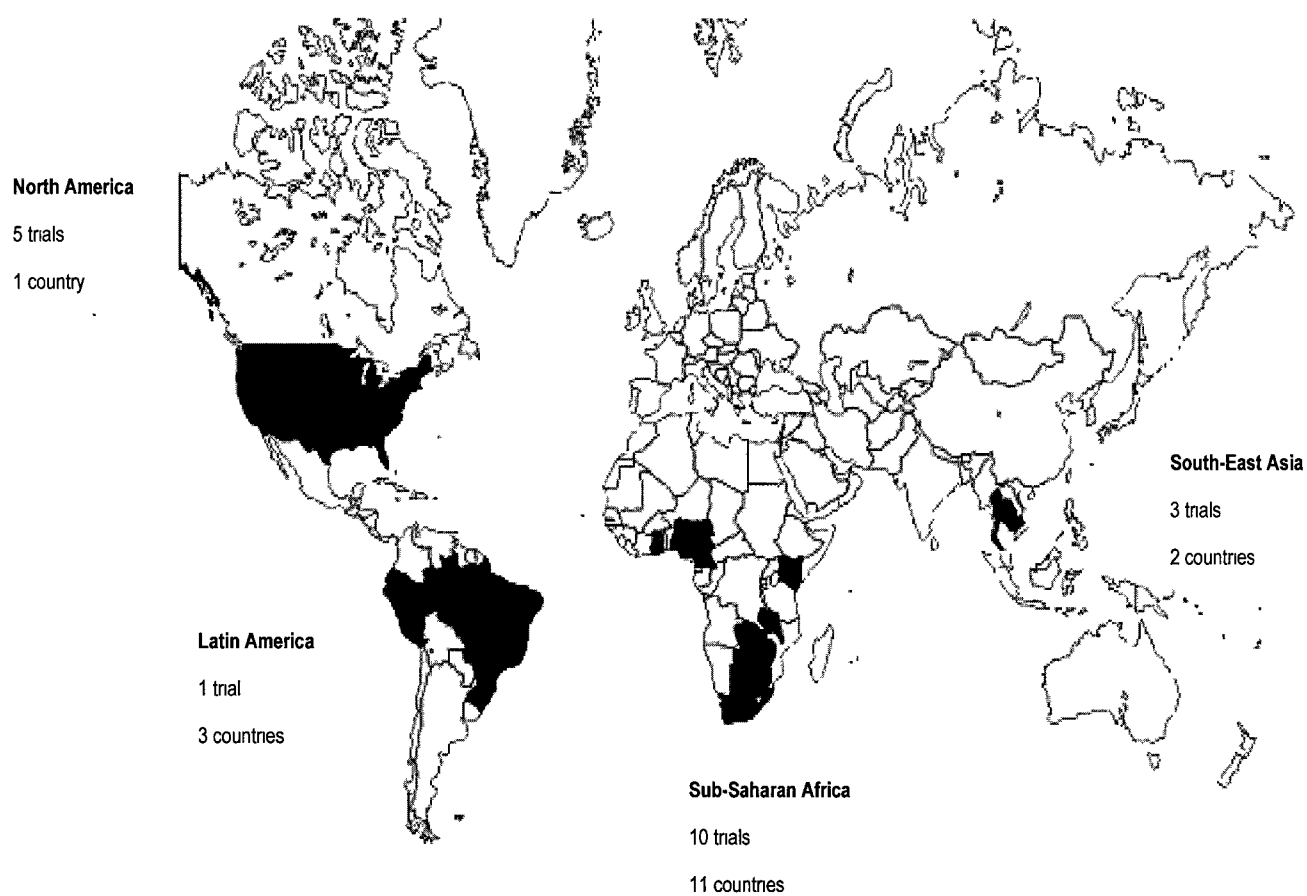


Figure 2. World map of countries considered for hosting PrEP trials



(http://english.freemap.jp/world_paint/world_paint.html)

Figure 3. Primary analysis: ethics appraisal (14 studies)

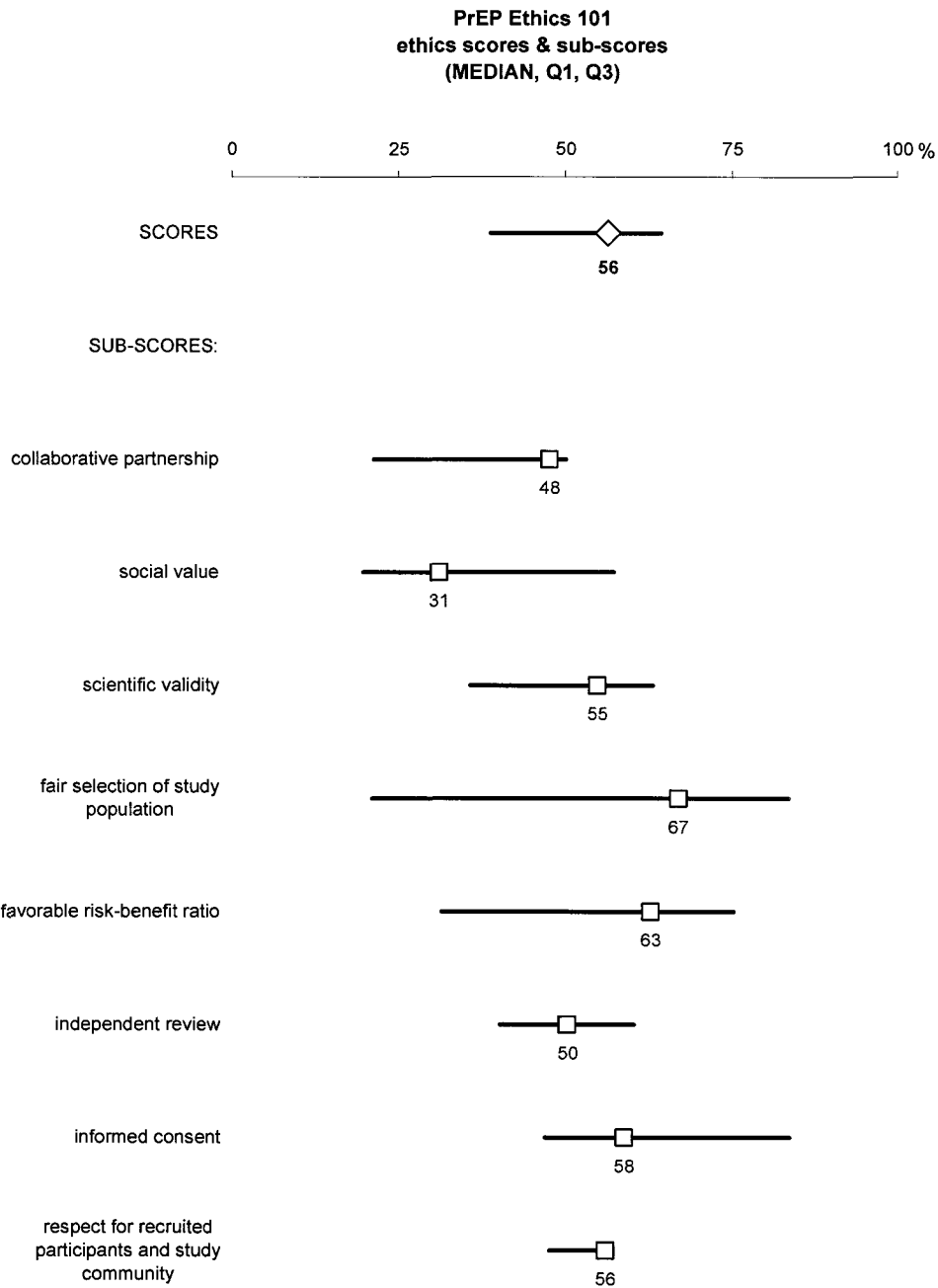
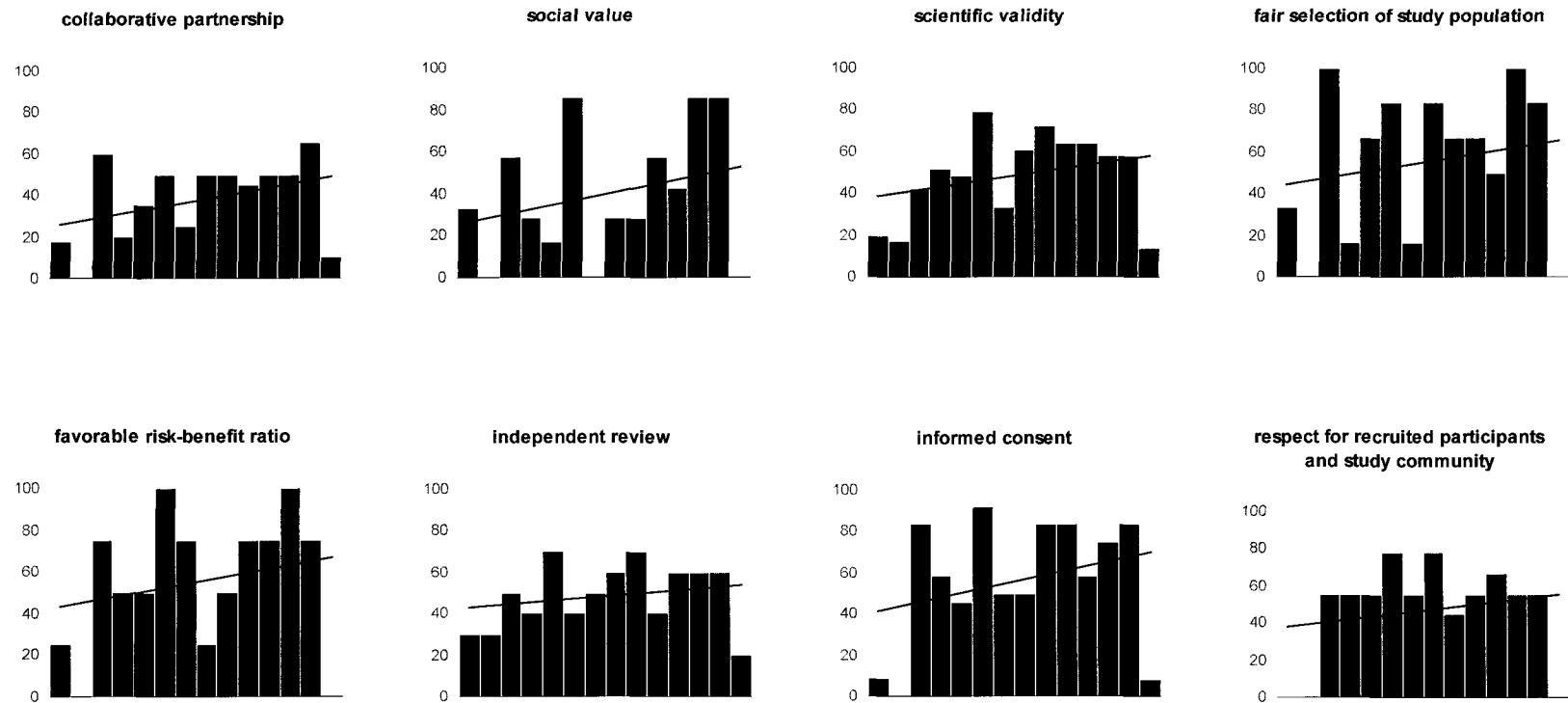


Figure 4. Primary analysis: variations in ethics sub-scores & time trends (14 trials)



Legend: - For each of the 8 ethics principles, a bar represents the ethics sub-score obtained by an individual study appraised (percentage of ethics considerations reported)..
 - The 14 studies appraised are chronologically ordered, based on the dates on sets of source documents reviewed (earliest study on left-hand side).
 - For each principle, a linear regression line was generated in Microsoft Excel®.

Figure 5. Sub-group analyses: quality scores (15 trials)

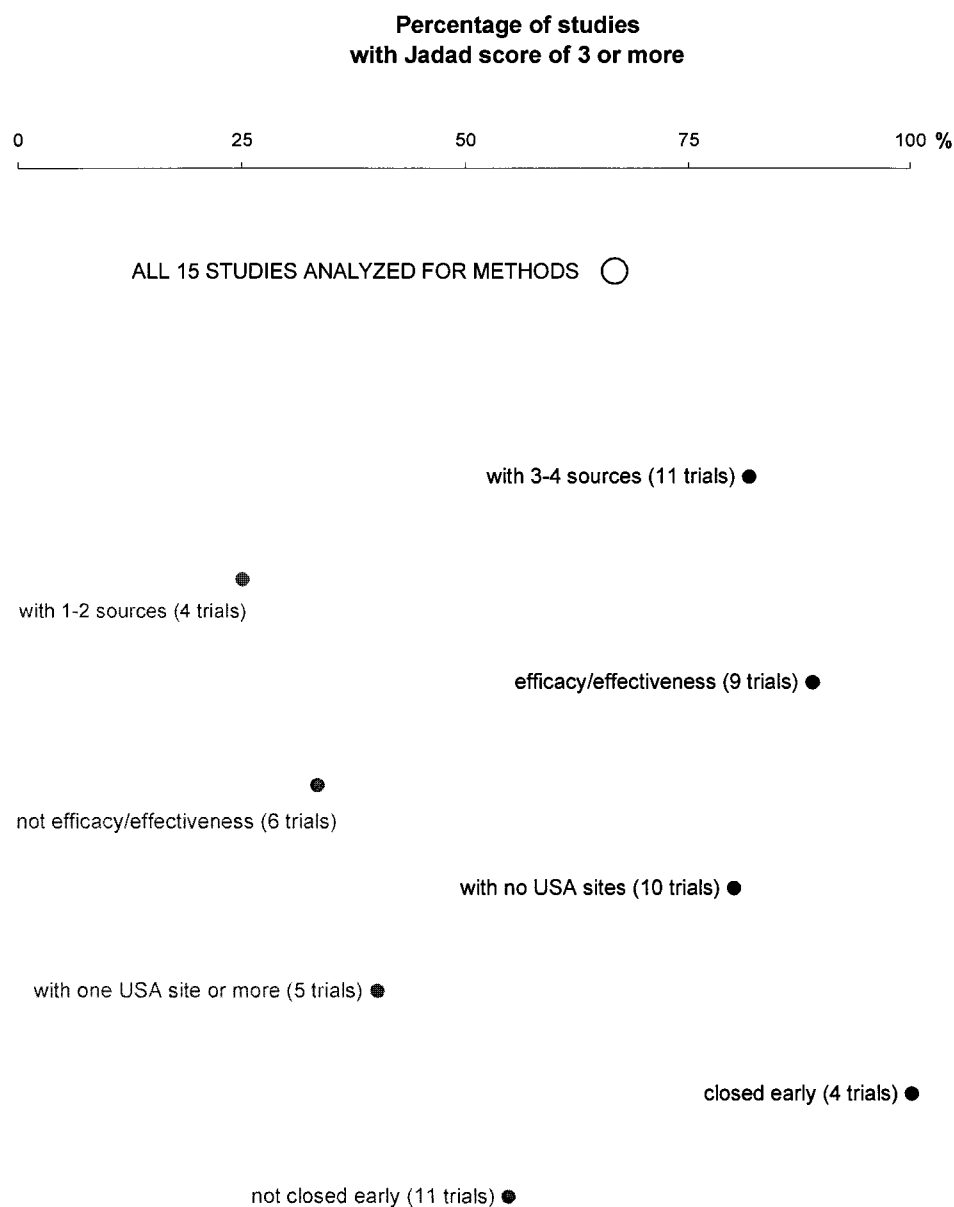
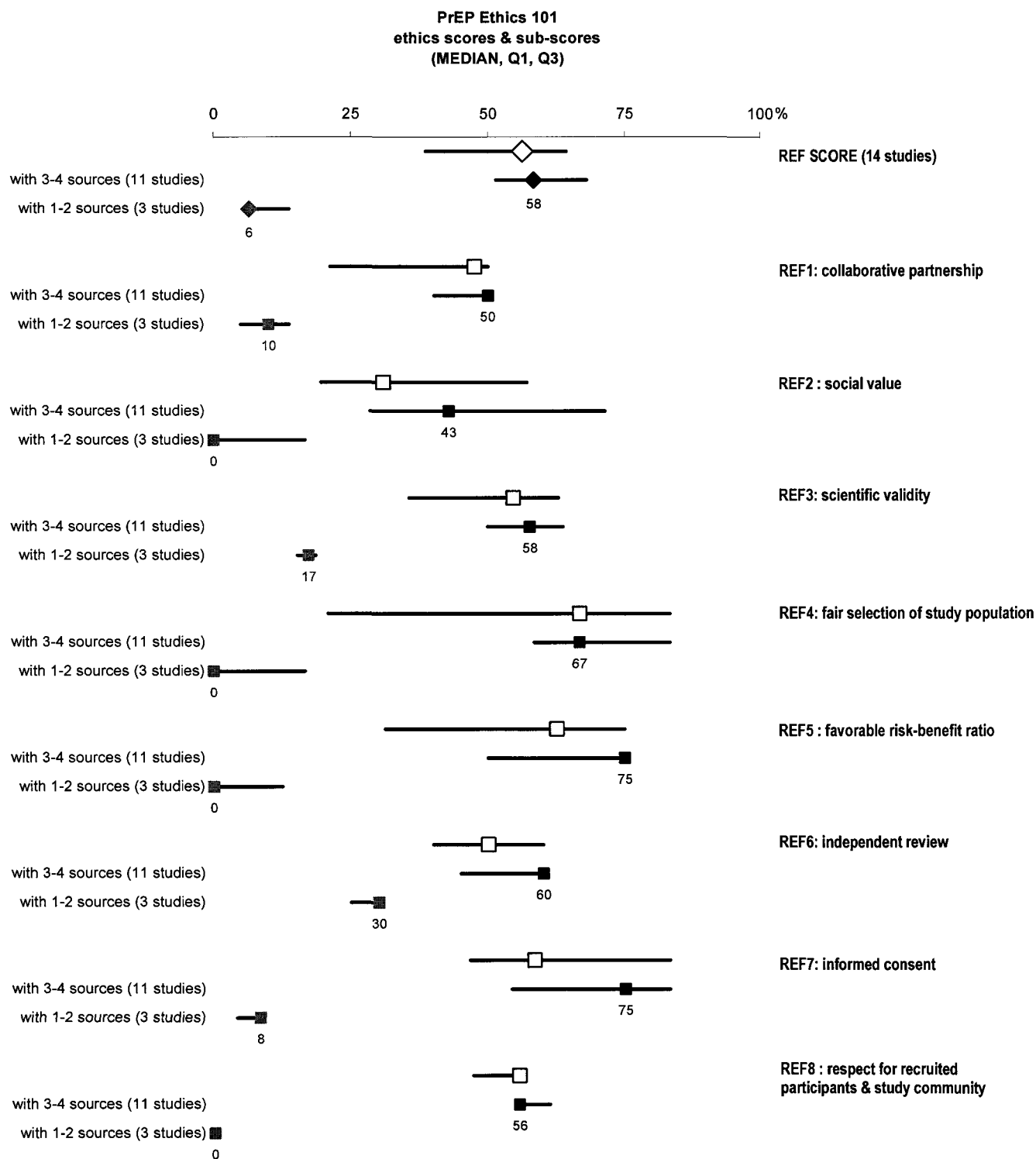
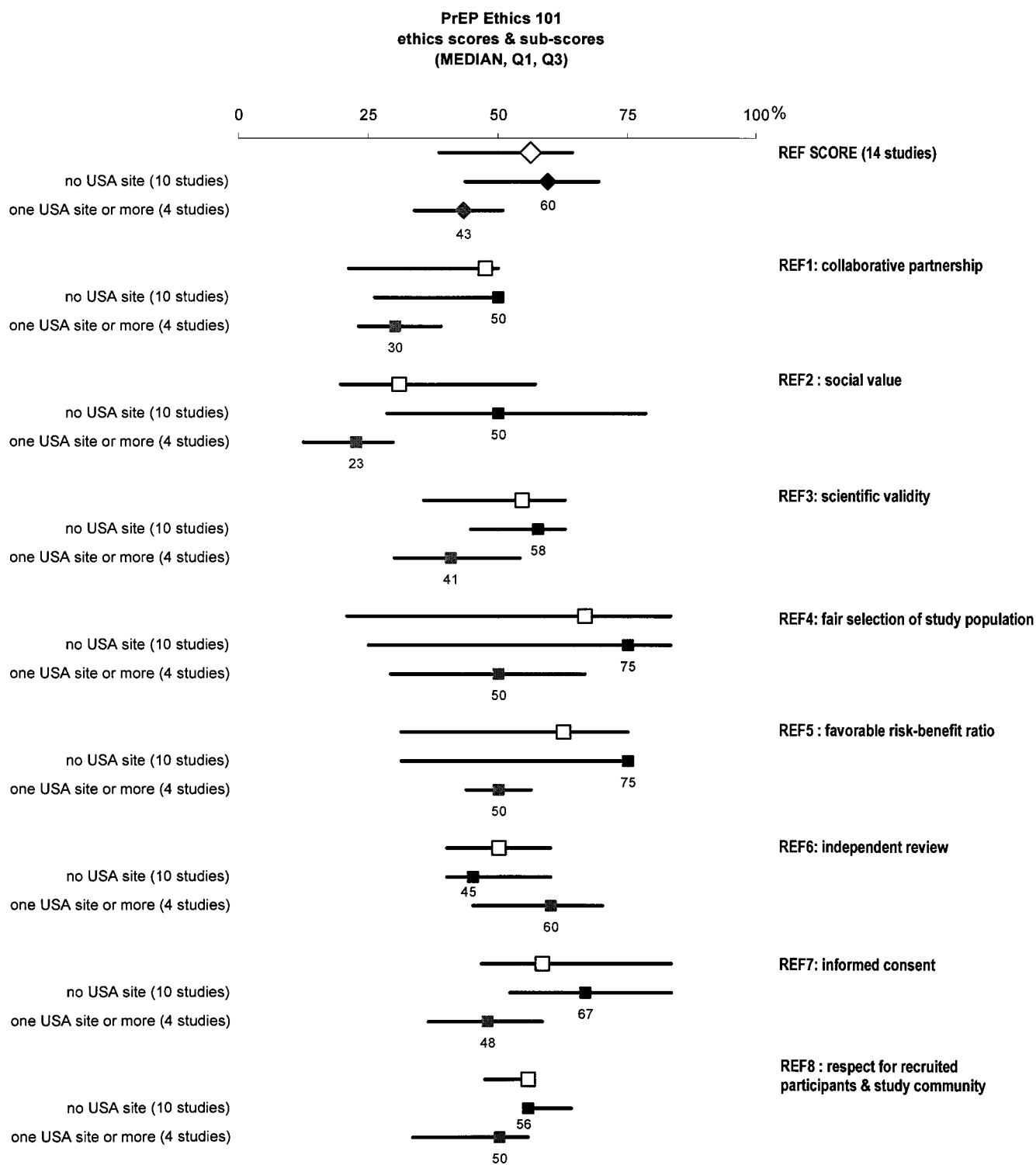


Figure 6. Sub-group analysis: studies with 3-4 sources (11 studies)



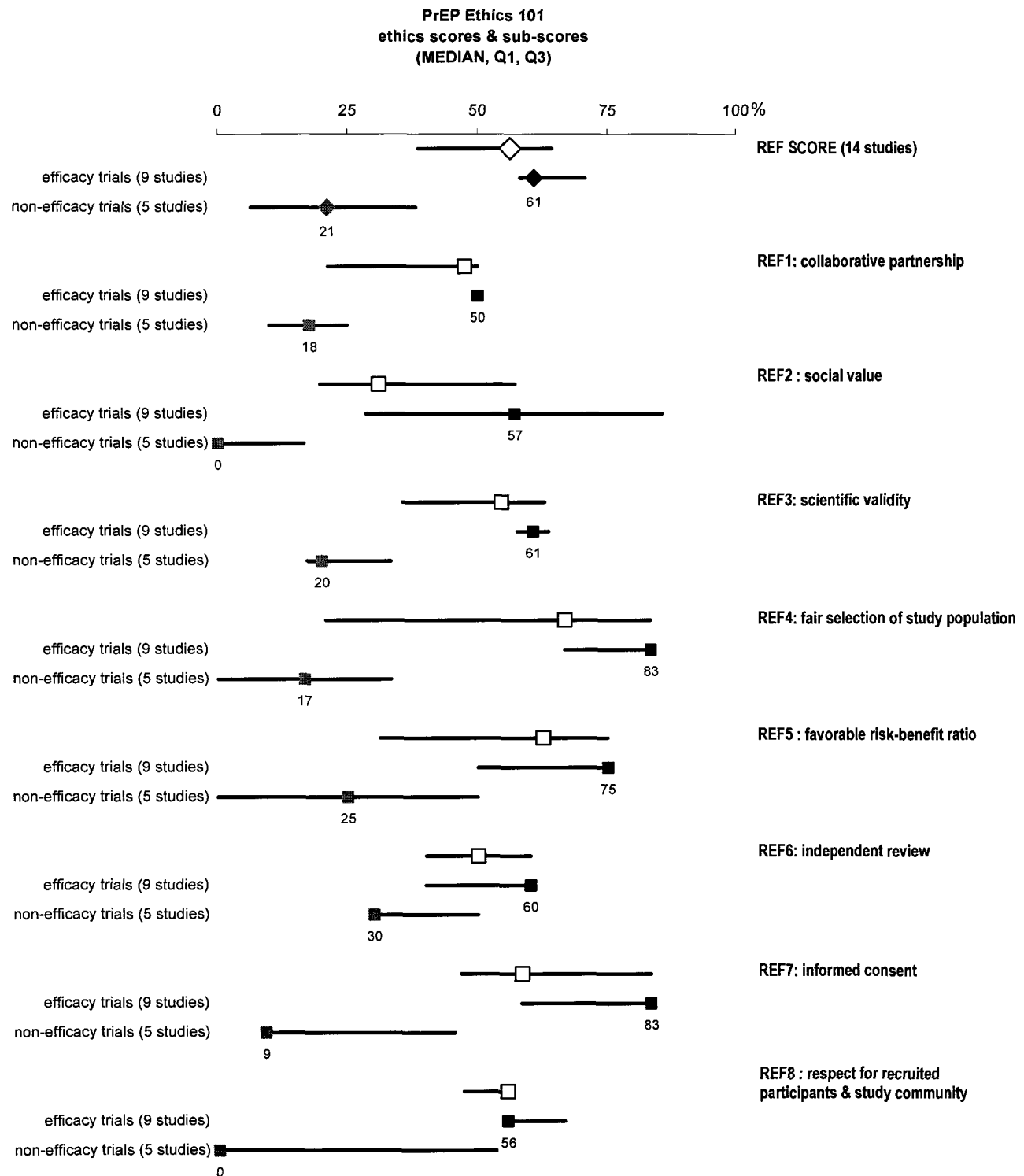
"REF" lines are medians of reference calculated for all 14 studies appraised.

Figure 7. Sub-group analysis: studies outside of the USA (10 studies)



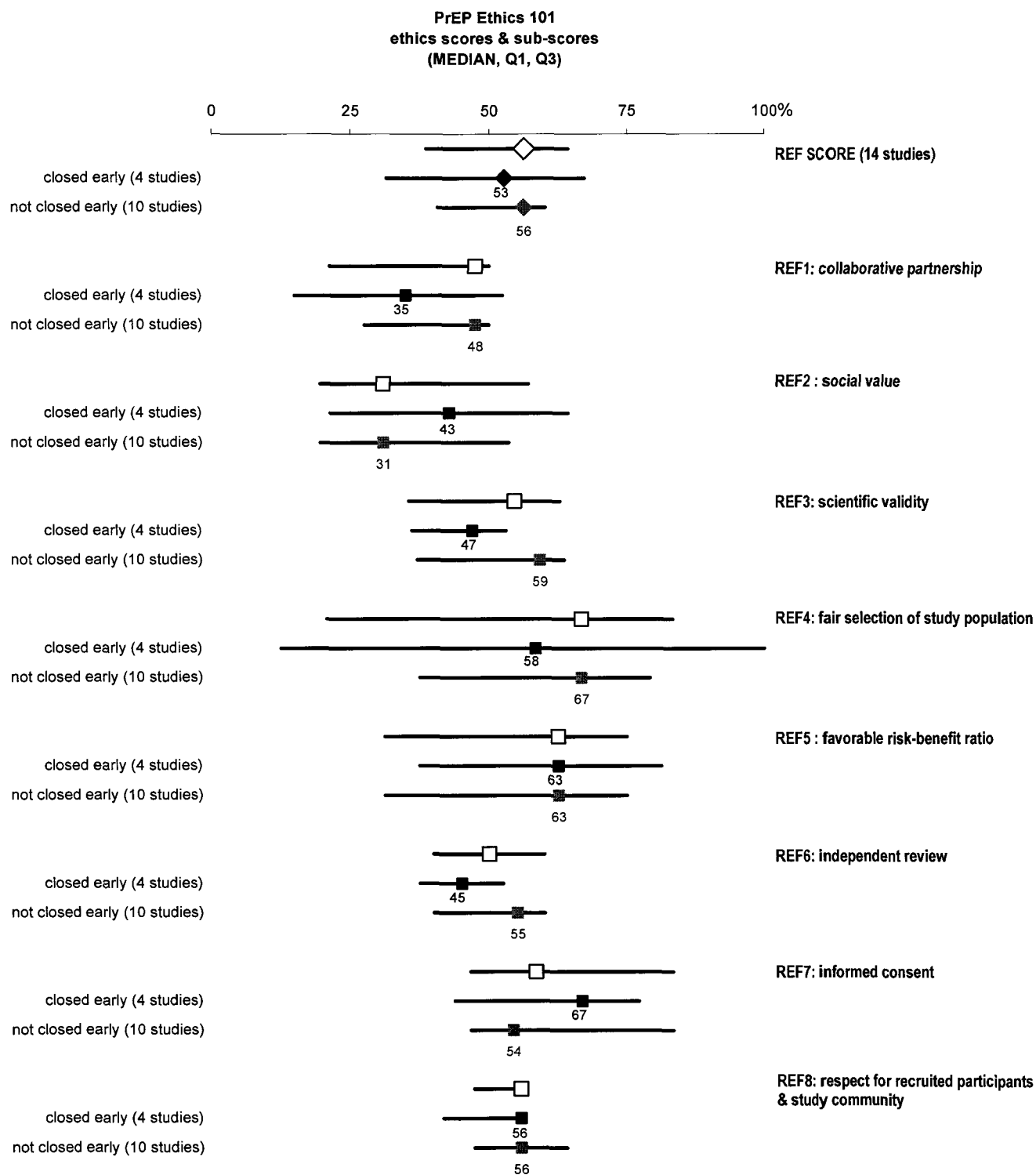
** REF * lines are medians of reference calculated for 14 all studies appraised.*

Figure 8. Sub-group analysis: efficacy/effectiveness as a primary question (9 studies)



"REF" lines are medians of reference calculated for all studies appraised.

Figure 9. Sub-group analysis: study sites closed early (4 studies)



"REF" lines are medians of reference calculated for all studies appraised.

Figure 10. Correlation ethics scores – Jadad scores (14 studies)

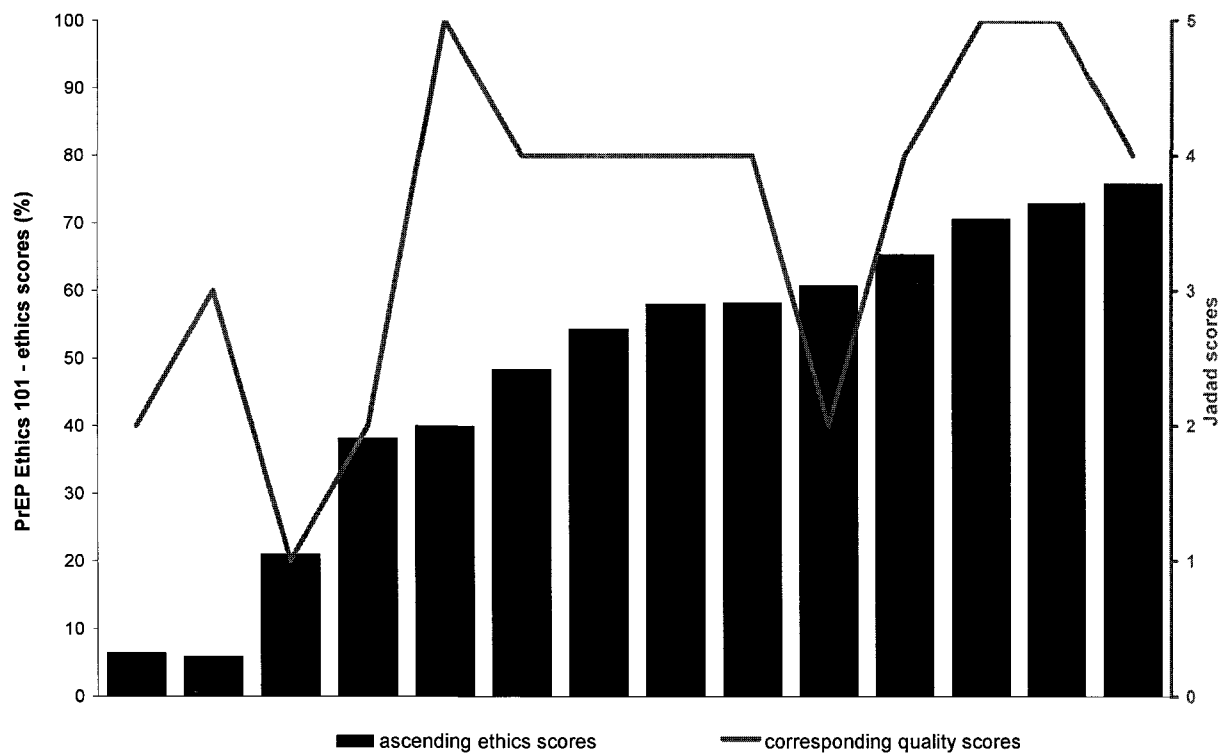


Figure 11. Synthesis: time trends for ethics scores and Jadad scores

Figure 11a Time trends: ethics scores and Jadad scores
(primary analysis: 14 studies)

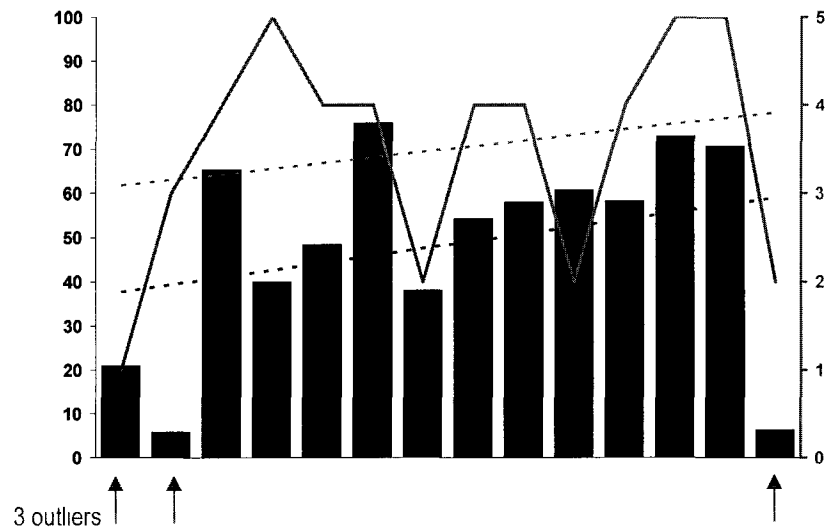
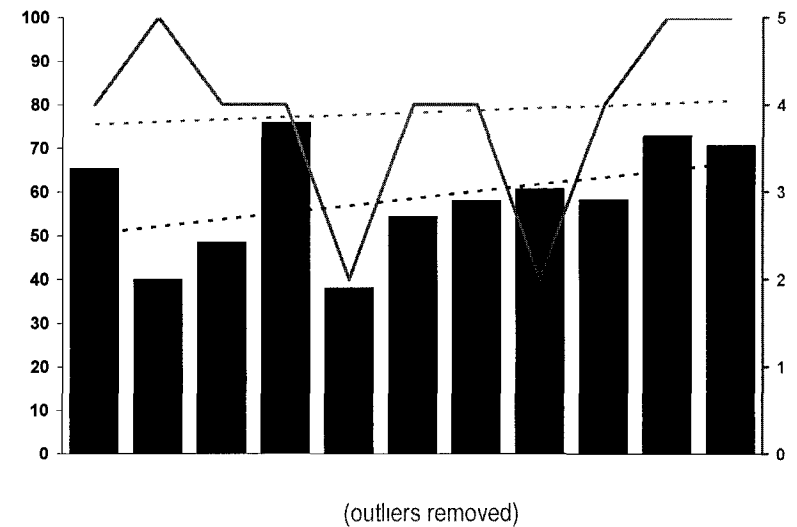


Figure 11b Time trends: ethics considerations and study quality
(outliers removed: 11 studies)



Legend ■ ethics scores (%) — — — Linear regression line (ethics scores)

— — — Jadad scores (1-5) — — — Linear regression line (Jadad scores)

- Each black bar represents the ethics score of an individual appraised study (percentage of ethics considerations reported)
- The studies appraised are chronologically ordered, based on the source documents dates (earliest study on left-hand side)
- Dotted lines are linear regression lines generated in Microsoft Excel® (black=ethics scores grey=Jadad scores)

Figure 12. Synthesis: past, current, and planned HIV oral PrEP trials (16 studies)



Size: *never enrolled; **planned size was 1,200

Population: ± couples: serodiscordant couples; IDUs: injecting drug users; MSMs: men who have sex with men

Test-drug: FTC=emtricitabine; NVP=nevirapine; TDF=tenofovir

Study timelines are represented as: a white area with a black frame (completed studies); a black area (ongoing studies); a grey area (studies in planning or not yet recruiting); or a striped area (sites/studies closed early). Numbers in those areas correspond to projected/actual start month and end month. Questions marks indicate that dates were not found in reviewed documents.

13.0 OTHER APPENDICES

Appendix 1. Search strategies

WORLD WIDE WEB

Google (main) engine (www.google.com)

HIV pre-exposure prophylaxis

SPECIALIZED WEBSITES

PrEP Watch (prepwatch.org)

[PrEP Trials Table]

HIV Prevention Treatment Network (www.hptn.org)

[List of HPTN Studies by Research Area]

Microbicide Trials Network (mtnstopshiv.org/search/node/protocols)

[List of MTN studies]

TRIAL REGISTRIES

United States National Institutes of Health registry (www.clinicaltrials.gov)

Interventional Studies | "HIV Infections" |

MetaRegister of Clinical Trials (www.controlled-trials.com)

HIV AND (prevent% OR prophyla%) AND (antiretroviral% OR anti-HIV)

World Health Organization's International Clinical Trial Registry Platform (www.who.int/ictrp/en)

HIV AND prevent* OR prophyla* AND antiretroviral* OR anti-HIV

(records from the NIH registry, identified by a code formatted as NCT00000000, were excluded from screening)

Note: databases excluded from search in the MetaRegister

Databases 4, 5, 11, 17, 19, 21, 24, 27, and 28 were not searched, as deemed irrelevant.

1. ISRCTN Register - trials registered with a unique identifier
2. Hong Kong Health Services Research Fund
3. Action Medical Research
4. ILEX Oncology Inc
5. Leukaemia Research Fund
6. King's College London (UK)
7. Medical Research Council (UK)
8. Laxdale Ltd
9. National Health Service Research and Development Health Technology Assessment Programme (HTA)
10. Medical Editors' Trials Amnesty
11. National Institutes of Health (NIH) - randomized trial records held on NIH *ClinicalTrials.gov* website
12. NHS Trusts Clinical Trials Register
13. The Wellcome Trust
14. National Health Service Research and Development Programme 'Time-Limited' National Programmes
15. UK Clinical Trials Gateway
16. National Health Service Research and Development Regional Programmes
17. Alzheimer's Society
18. National Research Register (UK)
19. Arthritis Research Campaign
20. Schering Health Care Limited
21. British Heart Foundation
22. Sir Jules Thorn Charitable Trust
23. CTSU - trials being randomised by the Clinical Trial Service Unit, Oxford
24. South Australian Network for Research on Ageing
25. Canadian HIV Trials Network
26. The Health Foundation
27. Cardiosource
28. UK Co-ordinating Committee on Cancer Research
29. GlaxoSmithKline
30. US Department of Veterans Affairs Co-operative Studies Program

ELECTRONIC DATABASES

Medline and Medline Non-Indexed (OvidSP platform)

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.sh.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. (ANIMALS not HUMAN).sh.
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. exp CLINICAL TRIALS/
12. (clin\$ adj25 trial\$).ti,ab.
13. ((sing\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
14. PLACEBOS.sh.
15. placebo\$.ti,ab.
16. random\$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. exp HIV/
31. HIV Seronegativity/
32. (seronegativ\$ or HIV?negativ\$ or uninfected).mp.
33. or/30-32
34. exp Anti-HIV Agents/
35. (antiretroviral\$ or anti?HIV or ARV\$).mp.
36. (phosphonylmethoxypropyl?adenine or PMPA or tenofovir or TDF or viread).mp.
37. (amino?fluoro?hydroxymethyl?oxathiolan?yl?pyrimidin?one or emtricitabine or FTC or emtriva or covacril).mp.
38. truvada.mp.
39. or/34-38
40. (pre-expos\$ or PrEP).mp.
41. *Primary Prevention/
42. (prevent\$ or prophyla\$ or chemoprevent\$ or chemoprophyla\$).mp.
43. or/40-42
44. 29 and 33 and 39 and 43
45. limit 44 to ed=20090206-current date

Embase (OvidSP platform)

1. Clinical trial/
2. Randomized Controlled Trial/
3. Randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. Random allocation.tw.
11. Randomly allocated.tw.
12. Allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. Placebo\$.tw.
18. Prospective Study/
19. or/1-18
20. Case Study/
21. Case report.tw.
22. Abstract report/ or letter/
23. or/20-22
24. 19 not 23
25. exp Human Immunodeficiency Virus/
26. (seronegativ\$ or HIV?negativ\$ or uninfected).mp.
27. or/25-26
28. *Antiretrovirus Agent/ or Highly Active Antiretroviral Therapy/
29. (antiretroviral\$ or anti?HIV or ARV\$).mp.
30. (phosphonylmethoxypropyl?adenine or PMPA or tenofovir or TDF or viread).mp.
31. (amino?fluoro?hydroxymethyl?oxathiolan?yl?pyrimidin?one or emtricitabine or FTC or emtriva or covacril).mp.
32. truvada.mp.
33. or/28-32
34. (pre-expos\$ or PrEP).mp.
35. Prevention Study/ or *Primary Prevention/ or Chemoprophylaxis/
36. (prevent\$ or prophyla\$ or chemoprevent\$ or chemoprophyla\$).mp.
37. or/34-36
38. 24 and 27 and 33 and 37
39. limit 38 to ed=20090206 -current date

The Cochrane Central Register of Controlled Trials (CENTRAL)

1. exp HIV/
2. HIV Seronegativity/
3. (seronegativ\$ or HIV?negativ\$ or uninfected).mp.
4. or/1-3
5. exp Anti-HIV Agents/
6. (antiretroviral\$ or anti?HIV or ARV\$).mp.
7. (phosphonylmethoxypropyl?adenine or PMPA or tenofovir or TDF or viread).mp.
8. (amino?fluoro?hydroxymethyl?oxathiolan?yl?pyrimidin?one or emtricitabine or FTC or emtriva or covacril).mp.
9. truvada.mp.
10. or/5-9
11. (pre-expos\$ or PrEP).mp.
12. *Primary Prevention/
13. (prevent\$ or prophyla\$ or chemoprevent\$ or chemoprophyla\$).mp.
14. or/11-13
15. 4 and 10 and 14

Appendix 2. List of key informants contacted

Investigators:

1. J. Brooks Jackson, MD
2. Kimberly Page-Shafer, PhD
3. Kata L. Chillag, PhD and Lisa A. Grohskopf, MD, MPH
4. Michael T. Martin, MD, MPH
5. Irving Hoffman, PA, MPH
6. Dawn K. Smith, MD, MS, MPH
7. Michael Thigpen, MD, DTM&H, LCDR USPHS and Lynn A. Paxton, MD, MPH
8. Robert M. Grant, MD, MPH and Vanessa M. McMahan, BS
9. Connie Celum, MD, MPH and Jared Baeten, MD, PhD
10. Lut Van Damme, MD, MS, PhD and Jennifer Deese, MPH
11. Anatoli Kamali, MD and Heiner Grosskurth, MD
12. Sybil Hosek, PhD

Sponsors:

1. FHI: Beth Robinson, Deputy Director for Research Dissemination
2. NIH: Laura Cearnal, Patient Representative Service

Appendix 3. Ethics guidance documents screened

1. Nuremberg Code (Trials of War Criminals) – 1949 ³³
2. Belmont Report (US National Commission) – 1979 ³⁶
3. Good Clinical Practice Guideline (International Conference on Harmonisation) – 1996 ²³⁸
4. Declaration of Helsinki (World Medical Association) – 2000 ¹⁹⁴
5. Seven Ethical Requirements that Make Clinical Research Ethical (Emanuel) – 2000 ⁴⁹
6. Ethical Considerations in HIV Preventive Vaccine Trials (UNAIDS) – 2000 ⁹⁶
7. Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (Vol.I) – 2001 ⁴¹
8. Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (Vol.II) – 2001 ⁴²
9. International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS) – 2002 ²³⁹
10. Ethical Aspects of Clinical Research in Developing Countries (The European Group) – 2003 ²⁴⁰
11. Ethical Principles and Benchmarks for Multinational Clinical Research (Emanuel) – 2004 ⁹²
12. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Canada) – 2005 ⁴⁷
13. Handbook for Good Clinical Practice (WHO) – 2005 ²⁴¹
14. Universal Declaration on Bioethics and Human Rights (UNESCO) – 2006 ²⁴²
15. Ethical Considerations in Biomedical HIV prevention Research (UNAIDS/WHO) – 2007 ¹
16. Good participatory practice - Guidelines for Biomedical HIV Prevention Trials (UNAIDS/AVAC) – 2007 ⁹⁷
17. Index of Ethics Issues in HIV International Research (CAHR) – 2008 ¹⁴
18. International Ethical Guidelines for Epidemiological Studies (CIOMS) – 2008 ⁴³
19. Methodological Challenges in Biomedical HIV Prevention Trials (IOM) – 2008 ¹⁵
20. Declaration of Helsinki (World Medical Association) – 2008 ³⁵

Appendix 4. Reference documents for ethical analysis framework

Emanuel et al.'s 8 principles⁹²	UNAIDS's 19 ethical guidance points (GP)¹	IOM's 9 chapters of recommendations¹⁵
1. Collaborative partnership	GP 1. Development of Biomedical HIV Prevention Interventions	Chapter 2. Basic Design Features: Size, Duration, and Type of Trials, and Choice of Control Group
2. Social value	GP 2. Community Participation	
3. Scientific validity	GP 3. Capacity Building	Chapter 3. Design Considerations: Risk-Reduction Counselling
4. Fair selection of study population	GP 4. Scientific and Ethical Review	Chapter 4. Design Considerations: Pregnancy
5. Favorable risk-benefit ratio	GP 5. Clinical Trial Phases	Chapter 5. Design Considerations: Adherence
6. Independent review	GP 6. Research Protocols and Study Populations	Chapter 6. Design Considerations: Recruitment and Retention
7. Informed consent	GP 7. Recruitment of Participants	Chapter 7. Site Preparedness
8. Respect for participants and study communities	GP 8. Vulnerable Populations	Chapter 8. Estimating HIV Incidence
	GP 9. Women	Chapter 9. Performing Interim Monitoring and Analyzing Trial Results
	GP 10. Children and Adolescents	Chapter 10. Alternative Trial Designs
	GP 11. Potential Harms; GP 12. Benefits	
	GP 13. Standard of Prevention	
	GP 14. Care and Treatment	
	GP 15. Control Groups	
	GP 16. Informed Consent	
	GP 17. Monitoring Informed Consent and Interventions	
	GP 18. Confidentiality	
	GP 19. Availability of Outcomes	

Appendix 5. Emanuel et al.'s ethical principles and benchmarks

As per the original article⁹²

Principles	Benchmarks
Collaborative partnership	Develop partnerships with researchers, makers of health policies, and the community. Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system. Respect the community's values, culture, traditions, and social practices. Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise. Ensure that recruited participants and communities receive benefits from the conduct and results of research. Share fairly financial and other rewards of the research.
Social value	Specify the beneficiaries of the research—who. Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries—what. Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements. Prevent supplanting the extant health system infrastructure and services.
Scientific validity	Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research. Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled. Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure.
Fair selection of study population	Select the study population to ensure scientific validity of the research. Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value. Identify and protect vulnerable populations.
Favorable risk-benefit ratio	Assess the potential risks and benefits of the research to the study population in the context of its health risks. Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.

As per the original article⁹²

Principles

Benchmarks

Independent review

Ensure public accountability through reviews mandated by laws and regulations.

Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate.

Ensure independence and competence of the reviews.

Informed consent

Involve the community in establishing recruitment procedures and incentives.

Disclose information in culturally and linguistically appropriate formats.

Implement supplementary community and familial consent procedures where culturally appropriate.

Obtain consent in culturally and linguistically appropriate formats.

Ensure the freedom to refuse or withdraw.

Respect for recruited participants and study communities

Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.

Ensure that participants know they can withdraw without penalty.

Provide enrolled participants with information that arises in the course of the research study.

Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants at least as good as existing local norms.

Inform participants and the study community of the results of the research.

Appendix 6. “Modified” Jadad 5 point-scale

The Jadad scale was used as per the original article¹⁰⁴. Amendments were made for studies that had no report available, as indicated by text parts underlined twice (below).

- 1. Was the study described as randomized?** (this includes the use of words such as randomly, random, and randomization)
- 2. Was the study described as double blind?**
- 3. Was there a description of withdrawals and dropouts?**

SCORING THE ITEMS:

[As per the original article]

GUIDELINES FOR ASSESSMENT

1. Randomization

[As per original article]

2. Double blinding

[As per original article]

3. Withdrawals and dropouts

Participants who are to be included in the study but may not complete the observation period or may not be included in the analysis must be described. The number and the reasons for withdrawal must be estimated. If no withdrawals are expected, it should be stated in the source-document. If there is no statement on withdrawals, this item must be given no points.

Appendix 7. Other reviews of HIV oral PrEP trials

Lead author, year	Features
Cohen, 2007¹⁵⁵ PrEP trials cited: 7	NARRATIVE REVIEW (search terms reported, no selection flowchart): Cochrane Library, PubMed, conferences reports (CROI, IAS) - population: animal and humans sexually exposed to HIV, no children/adolescents, no serodiscordant couples - intervention: antiretroviral therapy to reduce infectiousness in seropositives, or as PrEP, or as post-exposure prophylaxis - outcomes: seroconversions, adherence, repeated treatment requests, behavioural disinhibition - study design: observational studies - limits: English only, "appropriate" sample size only
Landovitz, 2007¹⁵⁶ PrEP trials cited: 7	PRESENTATION SUMMARY - population: not specified - intervention: male circumcision, HIV PrEP, anti-HIV microbicides - comparator: not specified - outcome: not specified - study design: not specified
Lagakos, 2008¹⁵ PrEP trials cited: 6	EXPERTS' CONSULTATIONS & LITERATURE REVIEW - population: not specified - interventions: nonvaccine HIV biomedical prevention approaches - comparators: not specified - outcomes: methodological features - study designs: phase 2 and 3 trials

Lead author, year	Features
Padian, 2008⁷⁰ PrEP trials cited: 3	NARRATIVE REVIEW (search terms reported, no selection flowchart): Medline (PubMed), Cochrane Library, conferences reports ("<i>relevant</i>" websites), specialized websites (UNAIDS, WHO, non-governmental organizations, advocacy groups), content experts - population: not specified - interventions: HIV biomedical prevention approaches (physical barriers, STI control in seronegatives, male circumcision, microbicides, antiretroviral-based microbicides, prevention of mother-to-child transmission, oral PrEP, antiretroviral therapy in seropositives, vaccines) - comparator: not specified - outcome: effectiveness - study design: randomised controlled trials, "rigorously done" observational cohort studies - limit: none mentioned
Clauson, 2009¹⁵⁷ PrEP trials cited: 12	REVIEW: search strategy not specified - population: not specified - interventions: HIV oral PrEP - comparator: not specified - outcome: not specified - study design: not specified
Hillier, 2009¹⁵⁸ PrEP trials cited: 9	ORAL PRESENTATION - population: not specified - interventions: HIV oral PrEP, antiretroviral-based microbicides - comparator: not specified - outcome: not specified - study design: not specified
Okwundu, 2009⁷⁷ PrEP trials cited: 9	SYSTEMATIC REVIEW AND METANALYSIS: Medline (PubMed), Central, Embase, AIDSearch - population: seronegative commercial sex workers, individuals in serodiscordant relationships, intravenous drug users, men who have sex with men, sexually active young adults - intervention: tenofovir, emtricitabine/tenofovir or other HIV oral PrEP regimen - comparators: placebo or other eligible antiretroviral or no treatment - outcomes: HIV incidence, adherence, safety - study design: randomised controlled trials

Lead author, year	Features
Willyard, 2009 ¹⁵⁹	DISCUSSION (no search strategy reported)
Studies identified: 9	- population: not specified - interventions: HIV oral PrEP - comparator: not specified - outcome: not specified - study design: not specified

Appendix 8. HIV oral PrEP trials mentioned in previous reviews

Review HIV oral PrEP studies	Cohen 2007	Landovitz 2007	Lagakos 2008	Padian 2008	Clauser 2009	Hillier 2009	Okwundu 2009	Willyard 2009
Jackson					•		•	
Peterson	•	•	•		•	•	•	•
Page-Shafer	•	•			•			•
Grohskopf	•	•			•	•	•	•
Choopanya	•	•	•	•	•	•	•	•
Hoffman		•	•		•			
Smith	•				•	•		
Thigpen	•	•	•	•	•	•	•	•
Grant	•	•	•	•	•	•	•*	•
Celum					•	•	•	•
Hendrix								
Van Damme					•	•	•	•
Chirenje			•		•	•	•	•
Grosskurth								
Anton								
Hosek								

*author also listed study NCT00350324 which was expanded to Grant's study and is hence a duplicate

Appendix 9. Hypothetical validation process for ethics checklist

INITIAL STEPS

1) Identify the need for a guideline

Because ethics guidance on the *conduct* of HIV oral PrEP research already exists, my specific goal would be to develop evidence-based *reporting guidelines* for ethics considerations in PrEP study protocols (to implement existing guidance).

2) Review the literature

For content, I would do a systematic review of published documents discussing methods or ethics issues in HIV oral PrEP (Population=HIV seronegative humans; Intervention= HIV oral PrEP; Comparator=any; Outcome=any; Study design=media article, letter, editorial, discussion paper, abstract, conference proceedings, scientific report, fact sheet, expert guidance, or review). This would help draft an initial list of ethical considerations previously discussed by authors, from diverse perspectives.

For methods, I would review the most recent systematic review on reporting guidelines that I am aware of²⁴³. I would also seek expert advice from An- Wen Chan, coordinator of the SPIRIT initiative (*Standard Protocol Items for Randomized Trials*)²²⁶. As far as I know, this is the only evidence-based initiative for the development of reporting guidelines for protocols. This will help design my methodology.

3) Obtain funding for the guideline initiative

PRE-MEETING ACTIVITIES

4) Identify participants

I would define clear eligibility criteria for “experts”, such as: a) at least 5 years demonstrated experience with or expertise (occupational or personal) about HIV/AIDS. Based on my preliminary systematic reviews, and on active networking, I would establish a list of eligible experts.

I would invite about 30-40 persons to participate. They should form an international representative group of discussion including: scientists (e.g., clinical trialists, methodologists, psychosocial specialists, clinicians), theorists and moral authorities (e.g., ethicists, philosophers, religious authorities), administrators (e.g., ethics boards chairs, policy-makers), lawyers (e.g., human rights experts), community members (e.g., persons living with HIV, representatives of AIDS serving organizations, members of key populations at higher risk, members of Community Advisory Boards in PrEP trial host countries).

I would start by surveying recruited experts to determine whether they think that a checklist to assess ethics considerations reporting in HIV oral PrEP would be needed and whether they or their peers would use it. I would pursue the project only if a majority of respondents confirm the relevance of the initiative. I would then form a smaller interdisciplinary group (10 dedicated experts) that would be more involved in the technical aspects of the project.

5) Conduct a Delphi exercise

*“The Delphi method is a structured process of obtaining information from a group of experts by means of a series of questionnaires, each one refined based on the feedback from respondents on a previous version.”*²²⁸ This process would be web-based, for efficiency and cost minimization. I would initially present background information, based on my preliminary reviews (e.g., existing guidelines, ethical issues previously discussed). Then, I would submit the initial draft list of items and would ask participants to judge which items should remain on the list and whether any items should be added.

6) Generate a list of items for consideration at the face-to-face meeting

An amended checklist would be established once participants’ opinions converge towards a consensus and stabilize (after 3-5 rounds of discussions). All contributions would be justified and documented.

7) Prepare for a face-to-face meeting

FACE-TO-FACE CONSENSUS MEETING

8) Present and discuss results of pre-meeting activities and relevant evidence

We (the small group of experts) would present the results of the Delphi exercise. With the larger group, we would discuss the rationale for including items in the checklist, whether some items are more important than others, and whether/how items could/should be grouped in domains (e.g., by ethics principle) and if so, which set of principles should be used. We would also assign tasks for the next steps of the project (e.g., manuscript redaction, knowledge translation planning).

POST-MEETING ACTIVITIES

9) Develop the guidance statement & 10) Develop an explanatory document

The small group of experts would finalize the checklist as well as an explanatory document detailing the evidence basis for the checklist, how it was developed and how it should be used. The checklist would be piloted by non-experts (e.g., graduate students) and amended, as deemed necessary.

11) Develop a publication strategy

The smaller expert group would circulate the final version of the checklist to all participant experts. After considering all comments, the smaller expert group would plan for the publication of the checklist (scientific peer-reviewed journals, PrEP sponsors' websites, AIDS serving organizations' websites).

POST-PUBLICATION ACTIVITIES

12) Seek and deal with feedback and criticism

We would disseminate our product at public scientific events and we would monitor the literature for constructive feedback. I would be the contact person and I would consult with the smaller group of experts to manage correspondence related to feedback.

13) Encourage guideline endorsement

We would encourage checklist endorsement by sponsors, investigators, ethics boards, AIDS serving organizations and editors.

14) Support adherence to the checklist & 15) Evaluate the impact of the reporting guidance

We would support adherence to the checklist and would evaluate its uptake and impact.

16) Develop Web site

For visibility, we would develop a Web site with the full text of the checklist and its explanatory document, and with our contact information, so as to collect comments on an ongoing basis.

17) Translate guideline (if need is identified)

18) Update guideline regularly (every 2 years or as relevant)

(This hypothetical process is based on guidance by Moher et al.)²²⁸

Appendix 10. Glossary

ABC ⁸

Prevention strategies: **abstain** from penetrative sexual intercourse (also used to indicate delay of sexual debut); **be faithful** (reduce the number of partners or have sexual relations with only one partner); **condomize** (use male or female condoms consistently and correctly).

Adverse Event (AE) ²³⁸

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Ethics ²⁸

The discipline that describes the behaviours, practices, thinking, and moral values generally agreed to be acceptable to society.

Inhibitory concentration of 50% (IC₅₀) ¹⁵⁰

The concentration of a compound needed to reduce population growth of organisms, including eukaryotic cells, by 50% in vitro. Though often expressed to denote in vitro antibacterial activity, it is also used as a benchmark for cytotoxicity to eukaryotic cells in culture.

Injecting drug users (IDUs) ⁸

This term is preferable to *drug addicts* or *drug abusers*, which are seen as derogatory terms and which often result in alienation rather than creating the trust and respect required when dealing with those who inject drugs. UNAIDS does not use the term “intravenous drug users” because subcutaneous and intramuscular routes may be involved. It is preferable to spell out in full and not use the abbreviation. An acceptable alternate phrasing is *people who inject drugs*.

Key populations at higher risk of HIV exposure ⁸

UNAIDS does not use the term “high-risk group” because it implies that the risk is contained within the group whereas, in fact, all social groups are interrelated. (...) Membership of groups does not place individuals at risk, behaviours may. (...) UNAIDS prefers the term “key populations” because it emphasizes that these populations, while being important to the dynamics of HIV transmission in a setting, are equally essential partners for an effective response to the epidemic.

Metanalysis ⁸³

A statistical technique for combining the results of a number of individual studies to produce a summary result.

MSM ⁸

Abbreviation for “men who have sex with men” or “males who have sex with males”. This term is useful as it includes not only men who self identify as gay or homosexual and have sex only with other men but also bisexual men, and heterosexual men who may, nonetheless at times have sex with other men.

People living with HIV ⁸

It is preferable to use “people living with HIV” (PLHIV), since this reflects the fact that an infected person may continue to live well and productively for many years.

Risk ⁸

Risk refers to risk of exposure to HIV which may be high as a result of specific behaviours or situations. (...) Behaviours, not memberships, place individuals in situations in which they may be exposed to HIV. Some populations may be at increased risk of exposure to HIV.

Risk compensation OR risk enhancement ⁸

A compensatory increase in behaviours which can result in exposure to HIV brought on by reduced perception of personal risk, e.g., uptake of a 50% effective preventive HIV vaccine might tend to encourage abandoning condom use.

Sex worker ⁸

The term “sex worker” is intended to be non-judgmental, focusing on the conditions under which sexual services are sold. Alternate formulations are: “women/men/people who sell sex”. Clients of sex workers may then also be called “men/women/people who buy sex”. The term “commercial sex worker” is no longer used, primarily because it is considered to be saying something twice over in different words (i.e. a tautology).

Stigma ⁸

A mark or sign of disgrace or discredit.

Sponsor ²⁸

A person or organization who gives support (usually financial but not necessarily) to a project.

Systematic Review ⁸²

A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.

Universal access ⁸

Commonly used is the phrase working towards achieving the goal of universal access (not capitalized) to HIV prevention, treatment, care and support. This initiative is outlined in the *2006 Political Declaration on HIV/AIDS*.

Universal precautions ⁸

Standard infection control practices to be used universally in healthcare settings to minimize the risk of exposure to pathogens, e.g. the use of gloves, barrier clothing, masks and goggles (when anticipating splatter) to prevent exposure to tissue, blood and body fluids.

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ATTACHMENT 1

HOW ARE ETHICAL CHALLENGES ADDRESSED IN HIV PrEP TRIALS?

REVIEWER'S BROCHURE

Table of Content

Introduction.....	2
Contact Information.....	2
Background.....	3
Research Area	3
Research Topic.....	3
Research Question	3
Research Methods.....	4
Funding	4
Your Role as a Reviewer	4
Screening.....	5
Conciliation for Screening	5
Collection of Data Sources.....	6
Confirmation of Inclusion.....	6
Data Extraction	7
Conciliation for Data Extraction	7
Relevant Documentation.....	8
Background Documents.....	8
Information Sources	8
Search Outputs	8
Screening-Related Documents	8
Data Sources	8
Extraction Forms	8

Introduction

Thank you for accepting to be involved in this systematic review!

As a token of appreciation, you will be namely cited any publication using your contribution*.

This brochure summarizes this study's procedures and is to serve as a basic reference document. It will be formally reviewed with the principal investigator, and supporting documentation will be made available to you.

However, do not hesitate to communicate with the principal investigator at any time, if you need further clarification. Your feedback would also be much appreciated for the betterment of the study methods or of this brochure.

Contact Information

Ms. Madzouka Kokolo, principal investigator

Dr. Dean A. Fergusson, collaborator

Dr. William D. Cameron, collaborator

* Please, communicate with Principal Investigator if you would like to more involved so as to be a co-author.

Background

This section presents summarized information on the background of this research project. Full versions of supporting documents will be made available to you.

Research Area

Over 25 years after the initial outbreak of HIV/AIDS, there still is no cure, despite continuous and strenuous research initiatives. Some HIV **therapeutic oral antiretrovirals** appear to have a potential to **prevent** the infection if regularly taken by **seronegative** subjects who are **highly exposed** to the virus –based on research in animals, on mother-to-child transmission, and on persons recently exposed. This novel experimental approach is called **PrEP**, for pre-exposure (chemo)prophylaxis.

Due to the pressing need for a greater variety of HIV prevention options, a dozen HIV PrEP trials have been or are being conducted **in humans**, raising great **hopes** in the scientific community. Nonetheless, HIV PrEP trials also raised **ethical concerns** in participating communities –mostly in the **developing world**. There, a few trials have been the object of much public argument between advocacy groups and scientists. This led, in some cases, to the **premature termination** of the trials.

Research Topic

Ethical issues in HIV PrEP, whether they are real or perceived by stakeholders, do challenge the development and conduct of the studies, as well as their scientific validity. And, as others have pointed out, "(...)scientifically unsound research on human subjects is ipso facto unethical". Therefore, it is essential to consider both an analysis of the methodologies used (**scientific validity**) and an appraisal of how **ethical challenges** are dealt with, to draw any conclusion on the ethical evaluation of HIV PrEP trials.

Research Question

How are ethical challenges addressed in HIV pre-exposure prophylaxis trials?

Research Methods

In order to answer the aforementioned research question, a **protocol** for a systematic **methodological** review was developed.

A **systematic review** is a research method –or the result thereof– that identifies studies relevant to a specific question, appraises their quality and summarizes their results using a transparent scientific methodology.

The present systematic review is particular in three ways. It is essentially a **qualitative**, not a quantitative study. It does not focus on outcomes, as most systematic reviews do, but on **ethics-related methods**. And, because most targeted studies are currently ongoing or in planning, the main data source documents are not published reports –as it is the case for most systematic reviews– but **trial registry files, study protocols, and consent forms**.

Funding

This study project is part of a master's thesis in Epidemiology (University of Ottawa). The principal investigator is receiving a fellow's stipend from the Ottawa Health Research Institute, as a master's student at the University of Ottawa and as a research assistant at the Ottawa Health Research Institute.

Your Role as a Reviewer

This section presents summarized information on your role as a reviewer, for this research project. Further supporting documents will be made available to you.

As you may know, it is common practice in systematic reviews to have at least two reviewers. Reviewers independently screen search outputs and/or independently extract pre-defined data items from selected data sources. They then compare their findings and address any disagreement.

This process is to ensure that all targeted data items are captured as per the systematic review protocol, and it enhances the **internal validity** of the review.

Screening

You may or may not be involved in this part of the review process.

Search strategies were developed and run in selected information sources (trial registries, OvidSP, specialized websites). They can be reviewed with you **upon request**.

Search outputs were generated and safely filed.

Copies of the **search outputs** will be given to you electronically and/or as print-outs –as per your stated preference.

A decision tree for the classification of exclusions is presented in the **Screening Algorithm**. Your findings need to be entered electronically to facilitate the conciliation process. You will be provided with a template **Microsoft Excel® Screening Spreadsheet** for that purpose.

Copies of the aforementioned screening-related documents will be made available to you electronically and/or as print-outs –as per your stated preference. Each document will be reviewed with you and any clarification question will be answered.

POTENTIAL CHALLENGES - Screening:

- 1 hesitation about including a study
- 2 unfamiliar terms in records fields
- 3 difficulties classifying exclusions
- 4 numerous records

TIPS:

- 1 review protocol for inclusion criteria, these are also summarized on Data Extraction Form (page 2)
- 2 a quick internet search may help, if unsuccessful or in doubt, communicate with principal investigator
- 3 review screening algorithm
- 4 take breaks as needed

Conciliation for Screening

You will contribute to the conciliation related to screening only if you were involved in an independent screening process.

You will systematically compare your findings with the other independent reviewer(s). Disagreements will be addressed based on the systematic review **Protocol/Protocol Amendments**.

Copies of the Protocol and Protocol Amendments will be given to you electronically and/or as a print-out –as per your stated preference. If relevant, further **protocol amendments** may be discussed with the principal investigator, as deemed necessary. Any new protocol amendment will be justified and documented.

Collection of Data Sources

You may or may not be involved in this part of the review process.

Data sources need to be located and obtained from information sources.

This will be done through **trial registry** search (for trial registry files), through communications with involved HIV PrEP **investigators/sponsors** –by email, fax or phone- (for the protocols and consent forms), through electronic **journals** search or hand search (for clinical study reports), or through **internet** search (for either data source type).

A contact list for HIV PrEP investigators/sponsors was developed, and the libraries of the University of Ottawa and of The Ottawa Hospital, as well as the internet, are to be used for the acquisition of some of the data sources.

A copy of the Key Informants' Contact List will be made available to you electronically and/or as a print-out –as per your stated preference.

The principal investigator is responsible for gathering and safely filing copies of all selected data sources.

POTENTIAL CHALLENGES - Data Source Collection.

- 1 no access to electronic journals/ libraries
- 2 data source not located

TIPS:

- 1 communicate with principal investigator
- 2 search the internet, if unsuccessful, communicate with principal investigator

Confirmation of Inclusion

You will contribute to confirming inclusion of selected data sources if you were involved in the process of collecting data sources or if you are involved in data extraction.

You will systematically scan each obtained data source to ascertain the fulfillment of pre-determined eligibility criteria, and will communicate with the other independent reviewer(s) if you find any data source to be ineligible.

Disagreements will be addressed based on the systematic review **Protocol/Protocol Amendments**.

Copies of the **Protocol and Protocol Amendments** will be given to you electronically and/or as a print-out –as per your stated preference. If relevant, further **protocol amendments** may be discussed with the principal investigator, as deemed necessary. Any new protocol amendment will be justified and documented.

Data Extraction

You may or may not be involved in this part of the review process.

The principal investigator is responsible for gathering and safely filing copies of all selected data sources.

Copies of data sources for selected studies will be made available to you electronically and/or as print-outs –as per your stated preference.

A set of extraction forms was developed to capture pre-defined data items.

Copies of extraction forms will be given to you electronically and/or as print-outs.

Each extraction form contains instructions/clarifications, identified within the text or located in footnotes/endnotes. However, each form will be reviewed with you and any clarification question will be answered.

POTENTIAL CHALLENGES – Data Extraction:

- 1 a lot of information to go through
- 2 concern that you may miss data items
- 3 inability to fit relevant information in any section
- 4 discrepancy across source documents
- 5 concern about conciliation process

TIPS:

- 1 make cross-notes both in data source and on extraction form
- 2 get familiar with the extraction forms beforehand, and you will know what you are looking for
- 3 record an "Additional Note" (Section 10 of Data Extraction Form)
- 4 extract data item from most appropriate source* and record an Additional Note (Section 10)
- 5 a convenient system might be to include both data source (T=trial registry, P=protocol, C=consent form, R=report) and data source page (* for ethics items, short description otherwise) in cross-notes

Conciliation for Data Extraction

You will contribute to the conciliation related to data extraction only if you were involved in an independent data extraction process.

You will systematically compare your notes –from each extraction form for each selected study- with the other independent reviewer(s). Disagreements will be addressed based on the systematic review **Protocol/Protocol Amendments**.

[†] For the purpose of this review, descending ranking for "data sources appropriateness" is as follows: clinical study report, consent form, protocol, trial registry file

Copies of the Protocol and Protocol Amendments will be given to you electronically and/or as a print-out –as per your stated preference. If relevant, further **protocol amendments** may be discussed with the principal investigator, as deemed necessary. Any new protocol amendment will be justified and documented.

Relevant Documentation

*Relevant documents listed below will be made available to you either electronically and/or as print-outs –as per your stated preference. In case you are interested in knowing more about the research study –i.e., beyond the review process, further information and/or documentation can be obtained **upon request**.*

Background Documents

1. Study protocol
2. Protocol amendments
3. Review Progress Checklist

Information Sources

1. Key Informants' Contact List

Search Outputs

1. OvidSP combined deduped output (Medline, Medline Non-Indexed, Embase, CENTRAL)
2. Other outputs: trial registries, specialized websites

Screening-Related Documents

1. Screening algorithm
2. Microsoft Excel® screening spreadsheet

Data Sources

1. Trial registry files
2. Study protocols
3. Consent forms
4. Clinical study reports

Extraction Forms

1. Data Extraction Form
2. PrEP Ethics 101 (ethics analysis checklist)
3. Consent Content Analysis Form

Data Extraction Form

ATTACHMENT 2

*Systematic review identification code** _ _ _

Reviewer's initials _ _ _ _

Data extraction completion date (dd-mon-yyyy) _ _ - _ _ - _ _ _ _

Please, write clearly and avoid abbreviations.

It is recommended to code, in the margin, the source and page where the data item was found†.

1.	IDENTIFICATION OF SELECTED TRIAL	2
2.	VERIFICATION OF ELIGIBILITY CRITERIA	2
3.	STUDY TIMELINE & SETTINGS	3
4.	MATERIAL & STRUCTURAL SUPPORT	5
5.	DATA SOURCE DOCUMENTS	7
6.	SCIENTIFIC AND CLINICAL METHODS	8
7.	RESULTS	22
8.	QUALITATIVE ASSESSMENT	24
9.	LIST OF ATTACHMENTS	26
10.	ADDITIONAL NOTES	26

* Please, see the list of selected studies, in Reviewer's Binder

† Please, see Reviewer's brochure

1. IDENTIFICATION OF SELECTED TRIAL

**Key Data Sources Reviewer's binder trial registry file

1.1. Systematic review identification code _____**1.2. Study "short name"**

_____**1.3. Trial official title**

_____**1.4. Record in trial registry****1.4.1. NIH Clinical Trial Registry:** NCT _____ ☐ no**1.4.2. MetaRegister:** ☐ yes ☐ no**1.4.3. Other trial code(s):** ☐ yes ☐ no

_____**1.5. Grant:** ☐ not mentioned
_____**2. VERIFICATION OF ELIGIBILITY CRITERIA**

**Key Data Source trial registry file

2.1. Study population=HIV seronegative humans ☐**2.2. Intervention(s)= antiretroviral regimen(s)** ☐**2.3. Study design=controlled prospective study** ☐**2.4. HIV transmission mode targeted by prevention strategy= sexual transmission** ☐**2.5. At least one of the test-drugs was approved for distribution to the public (e.g., by FDA)** ☐

3. STUDY TIMELINE & SETTINGS

**Key Data Source: trial registry file, protocol

3.1. Study timeline**3.1.1. Trial registration date** (dd-mon-yyyy)

____-____-____

3.1.2. Trial start date/planned start date (dd-mon-yyyy)

____-____-____

3.1.3. Completion date/planned completion date (mon-yyyy)

____-____-____

3.1.4. Trial status***3.1.4.1. Planning phase**☐**3.1.4.2. Recruiting/Screening/Enrolling phase**☐**3.1.4.3. Intervention/Analysis phase**☐**3.1.4.4. On hold†**☐**3.1.4.5. Halted‡**☐**3.1.4.6. Completed**☐**3.1.5. Status date** (dd-mon-yyyy)

____-____-____

3.2. National affiliation of lead research team§**3.2.1. United States of America**☐**3.2.2. Other:**☐

* Note that the statuses may be named slightly differently in data source document

† i.e., suspended until further notice

‡ i.e., closed anytime before planned completion date, not based on protocol stopping rules

§ Based on reported affiliation of principal investigator(s)

3.3. Host country(ies)**3.3.1. Africa:**No ☐Yes ☐

- 1 ☐ Botswana 2 ☐ Cameroon 3 ☐ Ghana 4 ☐ Kenya 5 ☐ Malawi 6 ☐ Nigeria
 7 ☐ South Africa 8 ☐ Tanzania 9 ☐ Uganda 10 ☐ Zambia 11 ☐ Zimbabwe

12 ☐ **Other-Africa:** _____**3.3.1.1. African region(s) represented:**

- 1 ☐ North 2 ☐ South 3 ☐ West 4 ☐ East 5 ☐ Central

3.3.2. Asia:No ☐Yes ☐

- 1 ☐ Cambodia 2 ☐ Thailand

3 ☐ **Other-Asia:** _____**3.3.2.1. Asian region(s) represented:**

- 1 ☐ Caucasus 2 ☐ Central 3 ☐ East 4 ☐ South 5 ☐ Southeast

3.3.3. America:No ☐Yes ☐

- 1 ☐ Ecuador 2 ☐ Peru

3 ☐ **United States of America*:** _____4 ☐ **Other-America:** _____**3.3.3.1. American region(s) represented:**

- 1 ☐ North 2 ☐ South 3 ☐ Central

3.3.4. Other continent†:No ☐Yes ☐**3.4. HIV prevalence in host community(ies)‡**

- 1 ☐ Not mentioned/unknown 2 ☐ Mentioned for some study sites 3 ☐ Mentioned for all study sites
 4 ☐ Estimate(s) based on assumption(s) 5 ☐ Estimate(s) based on relevant data

* Specify states

† Specify country(ies)

‡ Prevalence at the local community (e.g., city, region) level or –at least– at the country level

4. MATERIAL & STRUCTURAL SUPPORT

**Key Data Source: trial registry file, protocol

4.1. Study sponsor(s)^{*}**4.1.1. None mentioned**☐**4.1.2. US governmental institution**☐**4.1.2.1. Center for Disease Control and Prevention (CDC)**☐**4.1.2.2. National Institutes for Health / NIH center, institute, office[†] or initiative[‡] (NIH):**☐**4.1.2.3. US Aid for International Development (USAID)**☐**4.1.2.4. Other:**☐**4.1.3. US non-governmental institution**☐**4.1.3.1. Bill and Melinda Gates Foundation (BMGF)**☐**4.1.3.2. Family Health International (FHI)**☐**4.1.3.3. Other:**☐**4.1.4. Non-US institution(s):**☐**4.2. Study collaborator(s)[§]****4.2.1. None mentioned**☐**4.2.2. Bioethics regulatory body(ies):**☐**4.2.3. Governmental institution(s):**☐

As indicated/labeled in source document

[†] For NIH centers, institutes and offices, please see list[‡] Those initiatives include the Microbicide Treatment Network (MTN) and the HIV Prevention Treatment Network (HPTN)[§] As indicated/labeled in source document

4.2.4. Non-governmental organization(s):☐

4.2.5. Pharmaceutical company(ies):☐

4.2.6. Research/Clinical institution(s):☐

4.2.7. Academic institution(s):☐

4.2.8. Community organization(s):☐

4.2.9. Other:☐

4.3. Disclosed material support**4.3.1. Not reported**☐**4.3.2. Amount of financial support (source):**☐

4.3.3. Nature of in-kind support (source):☐

5. DATA SOURCE DOCUMENTS

**ADMINISTRATIVE PROCEDURES Section 5 is to be filled by Principal Investigator

5.1. Collection of source documents*Approved study protocol: DATE[†]: ____-____-____ not obtained ☐ yes ☐1 ☐ trial registry2 ☐ electronic database3 ☐ worldwide web4 ☐ literature/handsearch5 ☐ personal communication6 ☐ serendipitous finding5.1.1. Approved consent form(s): not obtained ☐ yes ☐1 ☐ trial registry2 ☐ electronic database3 ☐ worldwide web4 ☐ literature/handsearch5 ☐ personal communication6 ☐ serendipitous finding5.1.2. Clinical study report/related paper by involved author(s): not obtained ☐ yes ☐1 ☐ electronic database2 ☐ worldwide web3 ☐ literature handsearch4 ☐ personal communication5 ☐ serendipitous finding5.1.3. Other: no ☐ yes ☐5.1.3.1. Public presentation/information: ☐1 ☐ worldwide web2 ☐ literature/handsearch3 ☐ personal communication4 ☐ serendipitous finding5.1.3.2. Related scientific publication(s) by uninvolved author(s): ☐1 ☐ electronic database2 ☐ literature handsearch3 ☐ worldwide web4 ☐ personal communication5 ☐ serendipitous finding5.1.3.3. Unpublished report ☐1 ☐ personal communication2 ☐ serendipitous finding5.1.3.4. Other: ☐

* Specify type and name of information source in space provided

† Enter date of protocol version extracted

6. SCIENTIFIC AND CLINICAL METHODS

**Key Data Sources: trial registry file, protocol, clinical study report

6.1. Trial phase1 ☐ Phase I 2 ☐ Phase II 3 ☐ Phase II/III 4 ☐ Phase III**6.2. Primary study question(s)**1 ☐ Efficacy 2 ☐ Effectiveness 3 ☐ Safety/Extended safety 4 ☐ Adherence5 ☐ Other: _____**6.3. Planned sub-study(ies):**No ☐ Yes ☐_____
_____**6.4. Study design**6.4.1. Randomized clinical trial ☐6.4.2. Non-randomized controlled trial ☐6.4.3. Other: ☐

6.5. Number of intervention group(s)

6.6. Number of comparison group(s)

* Please, specify sub-study name or focus as well as the sub-sample size.

6.7. Study population

- 6.7.1. Heterosexual men ☐
- 6.7.2. Heterosexual women ☐
- 6.7.3. Men having Sex with Men ☐
- 6.7.4. Serodiscordant couples ☐
- 6.7.5. Other: ☐
-

6.8. Study sample

6.8.1. Sample size: ☐ subjects ☐ couples _____, _____

6.8.2. Recruitment method

- 6.8.2.1. not described ☐
- 6.8.2.2. public advertisement/campaign ☐
- 6.8.2.3. healthcare institution-based recruitment ☐
- 6.8.2.4. community organization-based recruitment ☐
- 6.8.2.5. designated recruiting agent/agency ☐
- 6.8.2.6. other: ☐
-
-

6.8.3. Inclusion criteria (for study participants):**6.8.3.1. age range:** [_ _ - _ _]**6.8.3.2. current degree of exposure (sexual activity):** ☐**6.8.3.2.1. number of sexual partners:** _____**6.8.3.2.2. number of coitus:** _____**6.8.3.2.3. other:** _____**6.8.3.3. current HIV prevention method:** ☐0 ☐ none 1 ☐ mutual monogamy 2 ☐ male condoms 3 ☐ female condoms4 ☐ other: _____**6.8.3.4. current contraceptive method:** ☐1 ☐ hormonal 2 ☐ intra-uterine device 3 ☐ sterilization (participant or her partner)4 ☐ other: _____**6.8.3.5. current health:****6.8.3.5.1. adequate liver function:** _____ ☐**6.8.3.5.2. adequate kidney function:** _____ ☐**6.8.3.5.3. bone mineral density:** _____ ☐**6.8.3.5.4. current health-other:** ☐

6.8.3.6. other inclusion criteria: ☐

6.8.4. Exclusion criteria (for study participants):**6.8.4.1. language barrier** ☐**6.8.4.2. unwillingness or inability to give free consent** ☐**6.8.4.3. unwillingness or inability to comply with study schedule** ☐**6.8.4.4. unwillingness or inability to remain involved for the full duration of follow-up** ☐**6.8.4.5. unwillingness or inability to comply with intervention/control regimen** ☐**6.8.4.6. hepatitis B infection:** _____ ☐**6.8.4.7. pregnancy/maternity matters:** ☐1 ☐ current pregnancy 2 ☐ current breastfeeding 3 ☐ desire of pregnancy within follow-up period4 ☐ current use of contraceptive: _____5 ☐ other: _____**6.8.4.8. other exclusion criteria:** ☐**6.8.4.8.1. current health:**

6.8.4.8.2. medical/surgical antecedents: ☐

6.8.4.8.3. social history: ☐

6.8.4.8.4. other: ☐

6.9. HIV infection laboratory detection**6.9.1. Antibody detection**☐

- 1 ☐ Rapid HIV Test: _____ 2 ☐ Western Blot (WB) 3 ☐ ELISA (EIA)
 4 ☐ Radio-immuno-precipitation (RIPA) 5 ☐ Indirect immunofluorescence 6 ☐ Dual EIA assays*

6.9.2. Direct HIV detection☐

- 1 ☐ Antigen assays 2 ☐ acid tests (NAT)
 3 ☐ Viral load measure in blood 4 ☐ Viral load measure in semen
 4 ☐ Other: _____

6.9.3. Adequacy of HIV infection diagnostic method[†]

- 6.9.3.1. Screening:** 1 ☐ adequate 2 ☐ inadequate 3 ☐ unclear

- 6.9.3.2. Follow-up:** 0 ☐ same as screening 1 ☐ adequate 2 ☐ inadequate 3 ☐ unclear

- 6.9.3.3. Follow-up off test-drug:** 0 ☐ same as screening 0 ☐ same as follow-up
 1 ☐ adequate 2 ☐ inadequate 3 ☐ unclear

* To detect recent infection

[†] Based on consultation with laboratory methods expert TO BE FILLED BY PRINCIPAL INVESTIGATOR

6.10. Intervention(s)**6.10.1. Number of interventions (eligible/total tested):**

___ / ___

6.10.1.1. Non eligible intervention*:☐**6.10.2. Nucleoside Reverse Transcriptase Inhibitor (NRTI)**☐

- 1 ☐ **abacavir** [ABC]=Ziagen® 2 ☐ **didanosine** [ddI-EC]=Videx® 3 ☐ **emtricitabine** [FTC]=Emtriva®
 4 ☐ **lamivudine** [3TC]=Epivir® 5 ☐ **stavudine** [D4T]=Zerit® 6 ☐ **zalcitabine** [ddC]=Hivid®
 7 ☐ **zidovudine** [AZT]=Retrovir®

6.10.3. Nucleotide Reverse Transcriptase Inhibitor (NtRTI)☐

- 1 ☐ **tenofovir** [TDF]=Viread®

6.10.4. Nonnucleoside-Based Reverse Transcriptase Inhibitor (NNRTI)☐

- 1 ☐ **delavirdine** [DLV]=Rescriptor® 2 ☐ **efavirenz** [EFV]=Sustiva®, Stocrin®
 3 ☐ **nevirapine** [NVP]=Viramune®

6.10.5. HIV-1 Protease (Proteinase) Inhibitor (PI)☐

- 1 ☐ **amprenavir**=Agenerase® 2 ☐ **atazanavir** [ATV]=Reyataz® 3 ☐ **darunavir**=Prezista®
 4 ☐ **fosamprenavir**=Lexiva® 5 ☐ **indinavir**=Crixivan® 6 ☐ **ritonavir**=Norvir®
 7 ☐ **nelfinavir**=Viracept® 8 ☐ **saquinavir**=Invirase®, Fortovase® 9 ☐ **triplanavir**=Aptivus®

6.10.6. Fusion Inhibitor☐

- 1 ☐ **enfuvirtide**=T20®, Fuzeon®

6.10.7. CCR5 co-receptor antagonist☐

- 1 ☐ **maraviroc**=Selzentry®

6.10.8. Integrase Inhibitor☐

- 1 ☐ **raltegravir**

6.10.9. Combination of drugs☐

- 1 ☐ **Aluvia®**, **Kaletra®** = [lopinavir(LPV)/ ritonavir(r)] 2 ☐ **Combivir®** = [lamivudine (3TC)/ zidovudine(ZDV)]
 3 ☐ **Truvada®** = [emtricitabine (FTC)/ tenofovir (TDF)]

6.10.10. Other test-drug:☐

* Please, name intervention and explain why it is non-eligible

6.10.11. Eligible test-drug regimen* (#__ of __)1 ☐ Dosage: _____ 2 ☐ Frequency: _____3 ☐ Duration of intervention†: _____**6.10.11.1. Choice of drug product and regimen is evidence-based‡:** No ☐ Yes ☐**6.10.11.1.1. Type of evidence§**1 ☐ Efficacy¶: ☐ HIV-1 clades: _____ ☐ HIV-2 clades: _____2 ☐ Effectiveness 3 ☐ Safety 4 ☐ Adherence 5 ☐ Resistance profile6 ☐ Convenience†† 7 ☐ Cost-effectiveness 8 ☐ Other: _____9 ☐ Other approaches: _____**6.10.11.1.2. Level of evidence**1 ☐ Biologic plausibility 2 ☐ In-vitro studies 3 ☐ In-vivo (animal) studies 4 ☐ mathematical modeling4 ☐ Phase I trial(s) 5 ☐ Phase II trial(s) 6 ☐ Phase III trial(s) 8 ☐ Other: _____**6.10.12. On-product follow-up****6.10.12.1. Total number of scheduled visits:** _____**6.10.12.2. Total duration of follow-up‡‡:** _____**6.10.13. Off-product follow-up§§:** No ☐ Yes ☐

6.11. Comparator(s)**6.11.1. Placebo** ☐**6.11.2. Other active intervention:** ☐

6.11.3. No intervention ☐**6.11.4. Other:** _____ ☐* If there is more than one eligible test-drug, please, shortly describe the other ones under **Sub-Section 6.11 Comparators**.

† From first dose date through last dose date.

‡ As reported in data source document (e.g., biological plausibility, previous relevant research results), with or without duly cited reference.

§ Based on approval by regulatory body (e.g., FDA)

¶ Specify type(s) and strains, as mentioned in source document.

†† e.g., easy administration, easy storage/carry-around, covert use, no correlation with sex behavior

‡‡ From enrolment date to last visit date

§§ From date of last product intake to last visit.

6.12. Co-intervention(s)^{*}6.12.1. Behavioral risk-reduction counseling ☐6.12.2. Male condoms provision ☐ counseling for appropriate use of male condom ☐6.12.3. Female condoms provision ☐ counseling for appropriate use of female condom ☐6.12.4. Other: ☐

6.12.5. None ☐**6.13. Combined intervention(s)[†]**6.13.1. Group 1: none mentioned ☐ ☐

6.13.2. Group 2: none mentioned ☐ ☐

6.13.3. Group 3: none mentioned ☐ ☐

6.13.4. Group 4: none mentioned ☐ ☐

6.13.5. Group 5: none mentioned ☐ ☐

6.13.6. Group 6: none mentioned ☐ ☐**6.14. Concomitant intervention(s)[‡]**6.14.1. Intervention(s) allowed: not specified ☐ ☐

6.14.2. Intervention(s) not allowed: not specified ☐ ☐

^{*} i.e., intervention applied systematically to all participants in all groups[†] i.e., any treatment systematically added to test-drug within one group, within study context. Specify group name and additional treatment[‡] i.e., any treatment taken by participants during follow-up period, outside of study context

6.15. Outcome measure(s)**6.15.1. Outcome(s) for efficacy/effectiveness:**None ☐Yes ☐1 ☐ primary outcome2 ☐ secondary outcome3 ☐ tertiary/exploratory outcome**6.15.1.1. HIV seroconversions**☐**6.15.1.1.1. Breakthrough virus(es) testing**☐1 ☐ resistance 2 ☐ other: _____**6.15.1.2. Other efficacy/effectiveness outcome:**☐

6.15.2. Outcome(s) for safety/extended safety:None ☐Yes ☐**6.15.2.1. Physical/Physiological harm**☐**6.15.2.1.1. Clinically sensible adverse events*:**none assessed ☐Yes ☐1 ☐ primary outcome2 ☐ secondary outcome3 ☐ tertiary/exploratory outcome**6.15.2.1.1.1. cardiovascular system**not assessed ☐**6.15.2.1.1.1.1. sign(s):**☐**6.15.2.1.1.1.2. symptom(s):**☐**6.15.2.1.1.2. endocrine/metabolic system:**not assessed ☐**6.15.2.1.1.2.1. sign(s):**☐**6.15.2.1.1.2.2. symptom(s):**☐**6.15.2.1.1.3. hepato-digestive system:**not assessed ☐**6.15.2.1.1.3.1. sign(s):**☐**6.15.2.1.1.3.2. symptom(s):**☐**6.15.2.1.1.4. immune system:**not assessed ☐**6.15.2.1.1.4.1. sign(s):**☐**6.15.2.1.1.4.2. symptom(s):**☐

* ICH 1996 (§ 1.2): an adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

6.15.2.1.1.5. integumentary:	not assessed	☐
6.15.2.1.1.5.1. sign(s):		☐
6.15.2.1.1.5.2. symptom(s):		☐
6.15.2.1.1.6. musculoskeletal system:	not assessed	☐
6.15.2.1.1.6.1. sign(s):		☐
6.15.2.1.1.6.2. symptom(s):		☐
6.15.2.1.1.7. nervous system:	not assessed	☐
6.15.2.1.1.7.1. sign(s):		☐
6.15.2.1.1.7.2. symptom(s):		☐
6.15.2.1.1.8. renal and urinary:	not assessed	☐
6.15.2.1.1.8.1. sign(s):		☐
6.15.2.1.1.8.2. symptom(s):		☐
6.15.2.1.1.9. reproductive system:	not assessed	☐
6.15.2.1.1.9.1. sign(s):		☐
6.15.2.1.1.9.2. symptom(s):		☐
6.15.2.1.1.10. respiratory system:	not assessed	☐
6.15.2.1.1.10.1. sign(s):		☐
6.15.2.1.1.10.2. symptom(s):		☐
6.15.2.1.1.11. general health:	not assessed	☐
6.15.2.1.1.11.1. sign(s):		☐
6.15.2.1.1.11.2. symptom(s):		☐
6.15.2.1.1.12. other:	not assessed	☐
6.15.2.1.1.12.1. sign(s):		☐
6.15.2.1.1.12.2. symptom(s):		☐

6.15.2.1.2. Serious adverse events^{*}: not assessed ☐ **Yes** ☐

1 ☐ primary outcome 2 ☐ secondary outcome 3 ☐ tertiary/exploratory outcome

6.15.2.1.2.1. resulting in death ☐

6.15.2.1.2.2. life-threatening ☐

6.15.2.1.2.3. requiring inpatient hospitalization/prolongation thereof ☐

6.15.2.1.2.4. resulting in persistent or significant disability/incapacity ☐

6.15.2.1.2.5. congenital anomaly/birth defect ☐

6.15.2.2. Outcomes for psychological/social harm[†]: ☐

1 ☐ primary outcome 2 ☐ secondary outcome 3 ☐ tertiary/exploratory outcome

6.15.2.2.1. Psychological harm

6.15.2.2.1.1. outcome measure(s) for behavioral disinhibition[‡]: ☐

6.15.2.2.1.2. outcome measure(s) for other types of psychological harm:

6.15.2.2.2. Social harm

6.15.2.2.2.1. occurrences of separation/divorce ☐

6.15.2.2.2.2. occurrences of joblessness/loss of job ☐

6.15.2.2.2.3. occurrences of threats/assault ☐

6.15.2.2.2.4. other outcome measure(s) for social harm: ☐

6.15.2.3. Outcome measure(s) for other types of harm: no measure ☐ ☐

1 ☐ primary outcome 2 ☐ secondary outcome 3 ☐ tertiary/exploratory outcome

^{*} ICH 1996 (§ 1.50) i.e., untoward medical occurrence

[†] Related to participation in study and/or to HIV status disclosure

[‡] Increased risk-taking behavior such as decreased use of protective methods, increase in sexual activity or in number of sexual partners .

6.15.3. Outcome(s) for adherenceno measure ☐ ☐1 ☐ primary outcome 2 ☐ secondary outcome 3 ☐ tertiary/exploratory outcome**6.15.3.1. Subjective outcome-s^{*}:** ☐

6.15.3.2. Objective outcome-s[†]: ☐

6.15.4. Other outcome measure(s):none ☐ ☐1 ☐ primary outcome 2 ☐ secondary outcome 3 ☐ tertiary/exploratory outcome

6.16. Management of adverse events (AEs) and serious adverse events (SAEs)**6.16.1. Use of grading standard(s) for AEs/SAEs** ☐

6.16.2. Care plan for AE/SAE management is clearly explained ☐**6.16.3. Designed healthcare institution(s) for AE/SAEs management is namely identified[‡]** N/A ☐ ☐**6.16.4. Modalities of attribution of AE/SAE to test-drug(s) are discussed** ☐**6.16.5. Coordinates of contact person for SAE reporting are provided** ☐**6.16.6. Compensation plan for SAEs is presented** None mentioned ☐ Yes ☐**6.17. Drug discontinuation rule[§]**None mentioned ☐ Yes ☐**6.17.1. HIV seroconversion:** _____ ☐ T ☐ P**6.17.2. Hepatitis B infection:** _____ ☐ T ☐ P**6.17.3. compliance issue:** _____ ☐ T ☐ P**6.17.4. pregnancy:** _____ ☐ T ☐ P**6.17.5. breastfeeding:** _____ ☐ T ☐ P**6.17.6. AE/SAE:** _____ ☐ T ☐ P**6.17.7. Other:** _____ ☐ T ☐ P^{*} e.g., reported by participants[†] i.e., measured by research staff[‡] If care is not to be provided by study staff[§] T=temporary discontinuation (hold), P=permanent discontinuation

6.18. Statistical analyses/analytic plan**6.18.1. Sample size determination**Not explained ☐Explained ☐**6.18.1.1. Expected HIV incidence rate:** _____**6.18.1.1.1. Based on existing data:** ☐**6.18.1.1.2. Based on assumption:** ☐**6.18.1.1.3. Estimate not justified** ☐**6.18.1.2. Test-drug anticipated efficacy:** _____**6.18.1.2.1. Based on existing data:** ☐**6.18.1.2.2. Based on assumption:** ☐**6.18.1.2.3. Estimate not justified** ☐**6.18.1.3. Estimated withdrawals:** _____**6.18.1.3.1. Types of withdrawals considered*:** ☐**6.18.1.3.2. Based on existing data:** ☐**6.18.1.3.3. Based on assumption:** ☐**6.18.1.3.4. Estimate not justified** ☐**6.18.1.4. Other variable(s) in sample size determination:** ☐

* e.g., lost to follow-up, non-compliance, pregnancy...

6.18.2. Power analysis**6.18.2.1. For primary outcome(s)**

0 ☐ Not applicable 1 ☐ Not reported 2 ☐ Reported*: _____

6.18.2.2. For secondary outcome(s)

0 ☐ Not applicable 1 ☐ Not reported 2 ☐ Reported: _____

6.18.2.3. For tertiary/exploratory outcome(s)

0 ☐ Not applicable 1 ☐ Not reported 2 ☐ Reported: _____

6.18.3. Interim analysis(es)[†]:

None mentioned ☐ Yes ☐

6.18.4. Analytic approach:

None mentioned ☐ ☐

6.18.4.1. intention-to-treat

☐

6.18.4.2. per-protocol

☐

6.18.4.3. other:

☐

6.19. Study design flexibility**6.19.1. Possibility to change study features**

None ☐ ☐

1 ☐ Sample size

2 ☐ Duration of follow-up

3 ☐ Eligibility criteria

4 ☐ Other: _____

6.19.2. Stopping rules:

None ☐ ☐

1 ☐ Harm

2 ☐ Futility

3 ☐ Benefit

4 ☐ Other: _____

6.19.3. Other:

None ☐ ☐

* Please, specify outcome(s) and corresponding power value(s)

† Please, specify interim analysis focus and schedule

7. RESULTS

**Key Data Sources: protocol, clinical study report

7.1. NO PRIMARY REPORT**7.2. Participants flow**1 ☐ #screened: _____ 2 ☐ #enrolled/randomized: _____ 3 ☐ #analyzed^{*}: _____ 4 ☐ #analyzed[†]: _____**7.3. Participants baseline characteristics****7.3.1. No data available**

	G1 (n=): _____	G2 (n=): _____	G3 (n=): _____	G4 (n=): _____	G5 (n=): _____	G6 (n=): _____	TOTAL
# enrolled/randomized (men/women)							
Mean age (years) (men/women)							
Years of school ≤ 12 (%) (men/women)							
Mean # of sexual acts/month (men/women)							
Consistent condom use (%) (men/women)							
Past pregnancies (%)							
Current use of contraceptive (%)							
STI within past 6 months (%) (men/women)							

^{*} For primary outcome(s)[†] For secondary outcome(s)

7.4. Study Results**7.4.1. No data available**

	G1 (n=): _____	G2 (n=): _____	G3 (n=): _____	G4 (n=): _____	G5 (n=): _____	G6 (n=): _____	TOTAL
# of seroconversions							
At least 1 significant AE (#, p-value*)							
At least 1 significant SAE (#, p-value)							
SAEs related to regimen (#)							
Decreased condoms use (% of participants, p-value)							
Pregnancies (#)							
Days off-product (% follow-up duration)							
Withdrawals† (%) (participant-initiated)							
Withdrawals‡ (%) (research team-initiated)							

7.5. Operations

- 7.5.1. Number of study sites in protocol _____ actual _____
- 7.5.2. Number of host countries in protocol _____ actual _____
- 7.5.3. Sample size in protocol _____ actual _____
- 7.5.4. Total number of HIV seroconversions in protocol _____ actual _____
- 7.5.5. Interim analysis(es) actually performed N/A or unknown ☐ no ☐ yes ☐
- 7.5.6. Amendments to protocol: N/A or unknown ☐ no ☐ yes ☐

* p-value from hypothesis testing comparing experimental group to corresponding control

† e.g., drop-out, lost to follow-up

‡ e.g., test-drug permanent discontinuation

8. QUALITATIVE ASSESSMENT**Key Data Sources: protocol, clinical study report PERSONAL JUDGEMENT**8.1. Jadad score^{*}** _____**8.1.1. Randomization**8.1.1.1. Study described as randomized (1 point) ☐8.1.1.2. Randomization sequence generation described *and* appropriate (+1 point) ☐8.1.1.3. Randomization sequence generation not described or inappropriate (-1 point) ☐**8.1.2. Blinding**8.1.2.1. Study described as double-blind[†] study (1 point) ☐8.1.2.2. Double-blinding method described *and* appropriate (+1 point) ☐8.1.2.3. Double-blinding method not described or inappropriate (-1 point) ☐**8.1.3. Withdrawals[‡]**8.1.3.1. Withdrawals and drop-outs/expected withdrawals and drop-outs described (1 point) ☐**8.2. Risk of bias (Cochrane Collaboration's assessment tool)[§]**8.2.1. Allocation sequence adequately generated? ☐ YES ☐ NO ☐ UNCLEAR8.2.2. Allocation adequately concealed? ☐ YES ☐ NO ☐ UNCLEAR8.2.3. Knowledge of allocated interventions adequately prevented during the study?
☐ YES ☐ NO ☐ UNCLEAR

8.2.4. Incomplete outcome data adequately addressed?

☐ NOT APPLICABLE^{**} ☐ YES ☐ NO ☐ UNCLEAR

8.2.5. Reports of the study free of suggestion of selective outcome reporting?

☐ NOT APPLICABLE ☐ YES ☐ NO ☐ UNCLEAR

8.2.6. Study apparently free of other problems that could put it at a risk of bias?

☐ YES ☐ NO ☐ UNCLEAR8.2.7. Other potential bias: through over-estimated HIV incidence rate ☐

* If no clinical study report is available, base decision on statistical analyses plan described in protocol

† Both the participants and the outcome assessors are blinded to the group allocation.

‡ Expected withdrawals should include both participant-initiated and research team-initiated withdrawals

§ If no clinical study report is available, base your answers on methods described in protocol. Please, use space provided for justifications

** Select the NOT APPLICABLE option if no clinical study report is available.

8.2.8. Other potential bias: through contamination ☐

8.2.9. Other potential bias: through sub-optimal compliance ☐

8.2.10. Other potential bias(es): ☐

8.3. References of interest

None mentioned ☐

8.3.1. Bioethics guidelines/regulations ☐

8.3.1.1. Developed/used in host country:

8.3.1.2. Developed/used in lead research team's country of affiliation:

8.3.1.3. International guidelines:

8.3.2. Other references of interest

8.3.2.1. Other HIV oral PrEP trials: ☐

8.3.2.2. Other: ☐

9. LIST OF ATTACHMENTS

9.1. Forms attached

9.1.1. Consent Content Analysis Form **N/A** ☐

9.1.2. Ethics Appraisal for HIV Pre-Exposure Prophylaxis Trials (*PrEP Ethics 101*) N/A ☐ ☐

9.1.3. Consolidated Standards of Reporting Trials (CONSORT)* N/A ☐ ☐

9.1.4. Newcastle-Ottawa Quality Assessment Scale (NOS)[†] N/A ☐ ☐

9.1.5. Other: no ☒ ☐

9.2. Other attachment(s)

10. ADDITIONAL NOTES

CATEGORY	Source Page	NOTE

* This is a checklist to assess reporting quality of randomized controlled studies

† This is a checklist to assess reporting quality of non-randomized controlled studies

ATTACHMENT 3

PrEP ETHICS 101

Based on:

Emanuel et al.'s Benchmarks of Ethical Research¹
UNAIDS Ethical Considerations in Biomedical HIV Prevention Trials²
IOM's Methodological Challenges in Biomedical HIV Prevention Trials³

Data extraction completion date (dd-mon-yyyy) _____

Reviewer's initials: _____

NOTES & INSTRUCTIONS:

- refer to footnotes for details on and reference for item
- check the item if corresponding **information is clearly present** once or more in source document⁴ being reviewed **OR**
- check the item if it is **not applicable to/clearly not appropriate** in the study
- **note in margin** the data source code⁵ and page number(s) where information was located
- **count the total of items** checked for each of the 31 benchmarks and each of the 8 principles
- **compute total score**

SCORE: ___ items

¹ Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *The Journal of Infectious Diseases* 2004; 189(5):930-937

² Joint United Nations Programme for HIV/AIDS (UNAIDS), World Health Organization (WHO). Ethical Considerations in Biomedical HIV prevention research. 2007

³ Lagakos S, Gable A et al. Methodological Challenges in Biomedical HIV Prevention Trials. *Board on Global Health & Institute of Medicine*. 2008

⁴ Approved study protocol or approved consent form.

⁵ Suggested data source code: T=trial registry; P=protocol; C=consent form R=report. It is recommended to make corresponding cross-notes in the data source as well. E.g., As you read a protocol, you find on page 67 "An independent Data Safety Monitoring Board will review monthly safety reports". This fulfills item 3.2.15. In the left margin, next to item 3.2.15, note "P67". In the protocol, in the left margin next to the key sentence, make a short note such as "DSMB" (you may also want to highlight the key sentence).

1. COLLABORATIVE PARTNERSHIP (6 benchmarks)

/20 items

- 1.1. Development of partnership with researchers, policy-makers, and the community⁶** ___/4
- 1.1.1. strategy to ensure legitimacy of community partners chosen to represent host community⁷ ☐
 - 1.1.2. mention of partnership with clinicians/scientist(s) and with policy-makers in host country⁸ ☐
 - 1.1.3. mention of creative and flexible partnership with HIV and/or non-HIV networks⁹
 - 1.1.4. mention of strategy for combining safety information from concurrent trials of similar products¹⁰
- 1.2. Involvement of partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research¹¹, and integrating research into the health-care system** ___/7
- 1.2.1. community network/partners for the study are namely identified and their roles clearly defined¹² ☐
 - 1.2.2. active contribution of host community in the development of the study question¹³ ☐
 - 1.2.3. active contribution of local partners in trial planning¹⁴ ☐
 - 1.2.4. active contribution of local partners in trial conduct and monitoring¹⁵ ☐
 - 1.2.5. mention of a Community Advisory Mechanism (CAM)¹⁶ ☐
 - 1.2.6. consultation with community/stakeholders regarding sustainability of interventions locally¹⁷

⁶ Separate and overlapping groups of people who are infected and affected by HIV in various ways (...) [and] who are united around an identity, activity, (...) function (...). [or] different sectors of society that are part of a larger social structure, all of which [having] a stake in a biomedical HIV prevention trial and its outcomes. (...) "Community" could [also] (...) describe the specific locations for research, such as the neighbourhoods or sections of town where key populations live or congregate and from which research participants are recruited.

Source: Joint United Nations Programme on HIV/AIDS (UNAIDS), AIDS Vaccine Advocacy Coalition (AVAC). Good participatory practice - Guidelines for biomedical HIV prevention trials. 2007. Pages 36-39.

⁷ **UNAIDS GP2** The process for determining who will be credible and legitimate community representatives should be addressed through a preliminary consultative process between researchers and key members of the community in which the research is proposed to take place.

⁸ **UNAIDS GP3** The desired relationship is one of equals, whose common aim is to develop a long-term partnership through South-South as well as North-South collaboration that sustains site research capacity. (...) scientific exchange, and knowledge and skills transfer, between sponsors, researchers, communities and their counterparts, and the countries in which the research takes place, including in the field of social science.

⁹ **IOU R7-6** To facilitate access to suitable study populations or existing research infrastructure –with **cost sharing** benefiting both partners- while minimizing investment required to prepare site.

¹⁰ **IOU R9-5** Including the scientific advantages and disadvantages of sharing information, the timing and logistics of doing so, ethical concerns, and how to report the results from such trials.

¹¹ **IOU R7-3**

¹² **UNAIDS GP2** Partnership agreements should include a clear delineation of roles for (...) researchers and research staff. (p.18)

¹³ **UNAIDS GP5** Community members, policy makers, ethicists, and investigators in the country have determined that their residents will be adequately protected from harm and exploitation, and that the biomedical HIV prevention product development programme is necessary for and responsive to the health needs and priorities in their country.

¹⁴ **UNAIDS GP2** Failure to properly and genuinely engage communities early in the stages of research planning may result in an inability to properly conduct and complete important trials.

¹⁵ **UNAIDS GP5** The country and the community either have, or with assistance can develop or be provided with, adequate scientific and ethical capability and administrative and health infrastructure for the successful conduct of the proposed research. **UNAIDS GP12** There should be an ongoing iterative consultative process to facilitate local or national decision-making about the appropriate level of support, care, and treatment provided to potential and enrolled participants. **UNAIDS GP 17** Researchers, trial sponsors, countries, and communities should agree on a plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions.

¹⁶ agreed mechanisms for community input [that may include a] Community Advisory Board (...), open community or town-hall meetings, door-to-door campaigns, trial participants' groups, call-in radio shows (...), and suggestion boxes (...), focus groups discussions and in-depth interviews (...). Source: Joint United Nations Programme on HIV/AIDS (UNAIDS), AIDS Vaccine Advocacy Coalition (AVAC). Good participatory practice - Guidelines for biomedical HIV prevention trials. 2007. Pages 36-39.

1.2.7. consultation with community/stakeholders regarding sustainability of site, after trial completion¹⁸

1.3. Respect of community's values, culture, traditions, and social practices ___/3

1.3.1. standard ethics training given to research staff in all study sites¹⁹ ☐

1.3.2. intervention(s) deemed culturally appropriate for use among host community²⁰ ☐

1.3.3. strategies to minimize/reduce stigma/discrimination attached to target population²¹ ☐

1.4. Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise ___/2

1.4.1. mention of a research literacy program for host community²² ☐

1.4.2. mention of investment in host country human capacity and physical infrastructure²³

1.5. Ensure that recruited participants and communities receive benefits from the conduct and results of research ___/1

1.5.1. benefits for study participants/host community are clearly delineated²⁴ ☐

1.6. Share fairly financial and other rewards of the research²⁵ ___/3

1.6.1. intellectual property is shared with investigator(s) based in host country ☐

1.6.2. some/all data to be owned/co-owned by local institution/organization ☐

1.6.3. mention of other agreed sharing of reward ☐

¹⁷ IOM R3-3

¹⁸ IOM R7-5

¹⁹ **UNAIDS GP2** Research literacy programs that include ethics training for study staff can facilitate and enhance cooperation with civil society groups.

²⁰ **UNAIDS GP1** HIV prevention product development should ensure that products are appropriate for use among such populations, among which it will be necessary to conduct trials

²¹ **UNAIDS GP8** Steps taken to protect the rights, the dignity, the safety, and the welfare of the participants. **UNAIDS GP 11** This includes availability of ongoing psycho-social services, including counseling, social support groups, and legal support.

²² **UNAIDS GP2** Researchers may lack the requisite language, communication skills, and experience to respond to community concerns, while communities may be unfamiliar with research concepts (...), and may not define HIV prevention research as a priority. This underscores the need for "joint literacy", whereby researchers and community groups become sufficiently fluent in the requisite concepts and language to work productively together.

²³ **IOM R7-1** Capacity building, capacity strengthening (e.g., prepare a site, have a training plan for staff, have a mentoring plan for inexperienced investigators).

²⁴ **UNAIDS GP6** The protocol should (...) demonstrate how the candidate biomedical HIV prevention intervention being tested is expected to be beneficial to the population in which testing occurs. **UNAIDS GP12** The protocol should outline any services, products, and other ancillary interventions provided in the course of the research that are likely to be beneficial to persons participating in the trials.

²⁵ **UNAIDS GP12** Discussion should include representatives from relevant country stakeholders (...). It should address issues such as payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, channels and modalities, including delivery strategies, target populations, demand estimates, and supply chain requirements.

2. SOCIAL VALUE (4 benchmarks)

/07 items

- 2.1. Specify the beneficiaries of the research-who** ___/1
- 2.1.1. identification of the beneficiaries of the research ☐
- 2.2. Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries-what** ___/2
- 2.2.1. documented assessment of HIV burden in host community²⁶ ☐
- 2.2.2. description of social context in host community, as relevant to study conduct²⁷ ☐
- 2.3. Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements** ___/3
- 2.3.1. description of knowledge translation plan within host community²⁸ ☐
- 2.3.2. mention of long-term²⁹ partnership plan with stakeholder(s) based in host community³⁰ ☐
- 2.3.3. drug proven safe and effective to be made available and affordable to host community, post trial³¹ ☐
- 2.4. Prevent supplanting the extant health system infrastructure and services** ___/1
- 2.4.1. discussion on expected impact of trial on health-care system/services in host community³² ☐

3. SCIENTIFIC VALIDITY (3 benchmarks)

/33 items

- 3.1. Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research** ___/1
- 3.1.1. trial design³³ is informed by social and political study(ies) of host community³⁴ ☐

²⁶ **UNAIDS GP3** Characterisation of the local epidemic through prevalence/incidence studies and behavioural assessments.

²⁷ **UNAIDS GP8** Aspect of social context that create conditions for exploitation or increased vulnerability.

²⁸ This should include behavioral risk-reduction intervention used in study, if proven effective –**UNAIDS GP12**. **UNAIDS GP14** Clinical trials should be integrated into national prevention, treatment, and care plans so that services provided through clinical trials or arrangements brokered for trial participants serve to improve the health conditions of both the trial participants and the community from which they are drawn, and support and to strengthen a country's comprehensive response to the epidemic.

²⁹ i.e., beyond study completion and study result dissemination

³⁰ **UNAIDS GP3**

³¹ **UNAIDS GP1, UNAIDS GP14, UNAIDS GP19** (...) foster development of safe and effective biomedical HIV prevention products and ensure that they are produced and made readily and affordably available to the communities and countries where a product is tested. **UNAIDS Context** (p.12) It is imperative that appropriate financial arrangements are in place to implement agreements made between partners at the time a study is initiated.

³² **UNAIDS GP14** Clinical trials should be integrated into national prevention, treatment, and care plans so that services provided through clinical trials or arrangements brokered for trial participants serve to improve the health conditions of both the trial participants and the community from which they are drawn, and support and to strengthen a country's comprehensive response to the epidemic. **UNAIDS GP17** Evaluation of the impact of the trial on the vulnerabilities of the communities involved in the study.

³³ **IOM R10-1, 10-2 and 10-3** It might be an alternative design such as a partially blinded factorial design, a discordant couples design, a non-inferiority design, a cluster randomized trial, or a dynamic design.

³⁴ **UNAIDS GP8** A social and political analysis should be carried out early on in planning the research process, to assess determinants of vulnerability, such as poverty, gender, age, ethnicity, sexuality, health, employment, education, and legal conditions in potential participating communities. Findings from this analysis should inform the design of research protocols, which should be sensitive to emerging information on incidental risks of social harm throughout the course of a trial. Research protocols might also include ongoing independent monitoring of a trial in relation to its impact on the vulnerabilities of communities participating in the study.

- 3.2. Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the protection and the health-care interventions to which they are entitled** ___/29
- 3.2.1. references from previous research/scientific arguments³⁵ justifying conduct of the study □
 - 3.2.2. use of triangulation for estimation of HIV incidence rate³⁶ (sample size determination)
 - 3.2.3. description of strategies for achieving accrual rate goals and for maximizing retention³⁷
 - 3.2.4. plans for evaluation of effectiveness of recruitment plan³⁸
 - 3.2.5. scientific justification of test-drug(s) choice and intervention regimen(s) □
 - 3.2.6. statement justifying chosen comparator(s)³⁹ □
 - 3.2.7. use of both blinded and unblinded control groups⁴⁰
 - 3.2.8. randomized comparisons of behavioral risk-reduction interventions incorporated into design⁴¹
 - 3.2.9. quality control measures in the promotion -by research staff- of HIV prevention⁴² for participants⁴³ □
 - 3.2.10. behavioral co-intervention was field tested during planning phase⁴⁴
 - 3.2.11. scientific justification of study timeline⁴⁵ □
 - 3.2.12. strategy to monitor actual degree of exposure of selected participants during trial⁴⁶ □
 - 3.2.13. description of monitoring plan for adherence⁴⁷
 - 3.2.14. safety outcome measures include measures for psychological and/or social harm⁴⁸ □
 - 3.2.15. mention of a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)⁴⁹

³⁵ This includes biologic plausibility, pre-clinical research, animal research, clinical research on humans, and psychosocial research.

³⁶ **IOI R8-1** At least one source of data from the direct longitudinal follow-up of individuals in the trial setting –UNAIDS GP3 Corroborated by at least one other source.

³⁷ **IOI R6-2** Developing effective strategies to achieve accrual rate goals and to minimize losses to follow-up.

³⁸ **IOI R6-3** Inclusion of evaluations of the effectiveness of recruitment and retention strategies in future research plans.

³⁹ **UNAIDS GP15** The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been scientifically validated in comparable populations or approved by relevant authorities) i.e., why was it appropriate to compare test-drug to placebo, no intervention, other active intervention...

⁴⁰ **IOI R2-3**

⁴¹ **(IOI R3-1) OR** choice of behavioral risk-reduction intervention(s) is evidence-informed

⁴² This should include provision of high quality condoms and unbiased education on use thereof, as well as unbiased behavioral counseling. **UNAIDS GP13** National and international research oversight groups should evaluate the pros and cons of independent organizations implementing risk-reduction interventions in biomedical HIV prevention trials...

⁴³ **UNAIDS GP13** The provision of HIV risk reduction counseling should be monitored to ensure quality and to minimize the potential conflict of interest between risk-reduction goals and the biomedical prevention trial's scientific goals.

⁴⁴ **IOI R3-4**

⁴⁵ Visits schedule should at least facilitate early detection of HIV seroconversion, and detection of delayed seroconversion. Follow-up duration should take into consideration the potential for selection of resistant HIV strains.

⁴⁶ This should help characterize potential sex-related behavior changes. For example, the degree of exposure could be reported by participants (number of sexual encounters during previous week, etc).

⁴⁷ **IOI R5-1** Development and use of adherence measures that can capture different adherence patterns over time; **R5-2** triangulation for adherence estimates, detailed adherence information collected on random sub-sample; **R5-3** directly observed therapy not to be used for effectiveness trials; **R5-4** empirical evaluations of strategies to increase adherence during and after a clinical trial; **R5-5** detailed plans for monitoring, measuring, and analyzing adherence data, and steps to improve adherence if poorer than anticipated; **R5-6** provision of data on adherence to data monitoring committee; **R5-7** analysis of adherence and behavior as both outcomes in an HIV prevention trial and modifiers of the effect; **R5-8** use of stratified analysis, causal model, matched case-control.

⁴⁸ **UNAIDS GP11** Participation (...) may involve (...) psychological, and social risks. [This] may cause anxiety, stress, depression, as well as stress between partners in a relationship. (...) Participation, if it becomes publicly known, may also cause stigma and discrimination against the participant (...). (...) Women may be at heightened risk of domestic violence as a result of trial participation.

⁴⁹ **IOI R4-5** DSMB/DMC should get periodic safety updates for pregnant women on test-drug.

- 3.2.16. at least one-third of DSMB/DMC members are host country community members⁵⁰
- 3.2.17. clear statement that DSMB/DMC has the option of unblinding to insure participants' protection⁵¹
- 3.2.18. statement of basis and criteria for recommendation by DSMB/DMC to modify trial's size/duration⁵²
- 3.2.19. futility stopping rule relies on evidence of a sustained impact on cumulative HIV incidence⁵³
- 3.2.20. study will allow provision of information on both short and long-term benefits of intervention⁵⁴
- 3.2.21. HIV testing and treatment plan for potential participants'/participants' partners⁵⁵ ☐
- 3.2.22. specific consent for HIV testing test⁵⁶ ☐
- 3.2.23. each HIV testing test is to include pre-test and post-test counseling⁵⁷ ☐
- 3.2.24. description of care plan for potential participants screened HIV positive⁵⁸ ☐
- 3.2.25. description of care plan for HIV seroconverting participants⁵⁹ ☐
- 3.2.26. description of complete action plan for participants who become pregnant⁶⁰
- 3.2.27. "events-driven" approach for the statistical analysis⁶¹ (actual seroconversion cases)
- 3.2.28. primary analytic strategy is intention-to-treat for efficacy endpoint⁶²
- 3.2.29. potential impact of adherence is taken into account for statistical analyses⁶³

3.3. *Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure* ___/3

- 3.3.1. mention/description of extensive pretrial research in host community⁶⁴
- 3.3.2. mention of involvement of behavioral and social scientists in early planning stages⁶⁵

⁵⁰ **IOI R9-1** Should include scientists, ethicists, and lay people familiar with the community and local norms.

⁵¹ **IOI R9-2** In particular, when the efficacy data show no significant trends favoring one of the blinded arms, a DSMB/DMC should unblind itself as this might reflect an intervention that may be harming patients.

⁵² **IOI R9-3** If such changes are implemented, the protocol should also specify how investigators should evaluate the trial results.

⁵³ **IOI R9-4**

⁵⁴ **IOI R2-2**

⁵⁵ **UNAIDS GP18** The sponsor and researcher should have a mechanism for [female participants' sexual partners] to come forward to report possible negative consequences and make sure that they are notified of such, preferably by the female participants. Likewise, when participants become HIV positive, sexual partners at ongoing risk should be notified for referral to testing programmes and treatment facilities.

⁵⁶ **UNAIDS GP16** Informed consent, with pre- and post-test counseling, should also be obtained for any testing for HIV status conducted before, during, and after the trial.

⁵⁷ **UNAIDS GP16** Informed consent, with pre- and post-test counseling, should also be obtained for any testing for HIV status conducted before, during, and after the trial.

⁵⁸ **UNAIDS GP16** This should include referral to clinical and social support services.

⁵⁹ **UNAIDS GP16** This should include referral to clinical and social support services.

⁶⁰ **IOI R4-1** Monitor actual pregnancy rates, adjust sample size and trial duration if estimated rates are exceeded, follow all women who become pregnant regardless of whether test-drug is discontinued; **R4-2** option to resume study medication for female participants no longer pregnant or breastfeeding **R4-3** evidence basis for discontinuation rule with participants who become pregnant; **R4-4** interim analysis, trial modification to give pregnant participants access to drug post-analyses

⁶¹ **IOI R2-1** As a guard against inaccurate estimates, investigators should consider using an "events-driven" approach, by analyzing study results when the pre-specified number of enrolled subjects has become HIV infected.

⁶² **IOI R9-6** Secondary sensitivity analyses excluding subjects believed to have been HIV infected when they were randomized can be useful. However, investigators should not substitute such analyses for the primary analysis, unless such exclusions -and non exclusions- can confidently be made without error. **IOI R9-8** Investigators can include as-treated analyses as secondary analyses, but should interpret them cautiously, because of the possibility that such discontinuations represent a type of informative censoring.

⁶³ **IOI R5-8** Perform stratified analysis when adherence appears similar between study arms, postulate causal models and perform randomization-based analyses, perform matched case-control adherence analyses.

⁶⁴ **IOI R7-4** To develop accurate estimates of HIV incidence, participant accrual, retention, and pregnancy rates, and to develop and evaluate logistical and regulatory processes to be used during the trial.

3.3.3. consultations/strategies to ascertain technical and material *feasibility* of trial⁶⁶

□

4. FAIR SELECTION OF STUDY POPULATION (3 benchmarks)

/06 items

4.1. Select the study population to ensure scientific validity of the research

___/2

4.1.1. scientific justification of study population, in relation to internal validity⁶⁷

□

4.1.2. scientific justification of study population, in relation to generalizability of results⁶⁸

□

4.2. Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value

___/2

4.2.1. justification of study population, based on risk minimization⁶⁹

□

4.2.2. description of educational initiatives to inform host community -at large- about the study⁷⁰

□

4.3. Identify and protect vulnerable populations

___/2

4.3.1. acknowledgment that study population is vulnerable⁷¹

□

4.3.2. description of measures to minimize risk of exploitation of participants⁷²

□

5. FAVORABLE RISK-BENEFIT RATIO (2 benchmarks)

/04 items

5.1. Assess the potential risks and benefits of the research to the study population in the context of its health risks

___/3

5.1.1. HIV strain(s) targeted by study is/are an important public health problem in host community⁷³

□

5.1.2. strategy to explore test-drug(s) safety for pregnant women and their fetuses⁷⁴⁶⁵ IOM R3-2⁶⁶ UNAIDS GP3 Strategies to overcome (...) disparities and empower communities could involve: (...)capacity-building programmes in the science and ethics of biomedical HIV prevention research by relevant scientific institutions and local and international organisations; support to develop national and local ethical review capacity; (...) development of laboratory capacity that can support health care provision as well as research.⁶⁷ UNAIDS GP6 The selection of the research population should be based on the fact that its characteristics are relevant to the scientific issues raised.⁶⁸ UNAIDS GP6 The research protocol should justify the selection and size of the research population from a scientific point of view. This should consider the target viral strain, the target population, the target HIV transmission mode, the target health system (availability of drug to healthcare administration, roll-out capacity, etc).⁶⁹ UNAIDS GP7 Selection and recruitment of communities and individuals for participation in a trial must be fair and should create a research climate which shows respect for all persons. (...) The scientific goals of the study should be the primary basis for determining the individuals who will be recruited and enrolled.⁷⁰ UNAIDS GP3 Given the long time frames of biomedical HIV prevention research, special attention to communication and transparency is needed in order to build and maintain trust with participating communities, and to sustain site capacity even after the end of a trial.⁷¹ UNAIDS GP7 Vulnerability is based on social and cultural factors or on social marginalization, political powerlessness, and economic dependence. UNAIDS8 Examples of populations that may have an increased vulnerability include women, children and adolescents, men who have sex with men, injecting drug users, sex workers, transgender persons, indigenous populations, the poor, the homeless, and communities from resource-poor settings in high-income and low- and middle-income countries.⁷² UNAIDS GP8 The research protocol should describe the social contexts of a proposed research population (country or community) that create conditions for possible exploitation or increased vulnerability among potential trial participants, as well as the steps that will be taken to overcome these and protect the rights, the dignity, the safety, and the welfare of the participants.⁷³ UNAIDS GP5 Establishing a biomedical HIV prevention product development programme that entails the conduct of some, most, or all of its clinical trial components in a country or community that is relatively vulnerable to harm or exploitation is ethically justified if: the product is (...) anticipated to be effective against a strain of HIV that is an important public health problem in the country.⁷⁴ IOM R4-2

5.1.3. participants who become pregnant are followed whether drug is discontinued or not⁷⁵

5.2. Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations ___/1

5.2.1. statement/discussion about risk-benefit ratio⁷⁶ ☐

6. INDEPENDENT REVIEW (3 benchmarks)

 /10 items

6.1. Ensure public accountability through reviews mandated by laws and regulations⁷⁷ ___/3

6.1.1. reference to bioethics laws/regulations in host country or acknowledgement of absence thereof⁷⁸ ☐

6.1.2. reference to protocol review/approval process by ethics committee⁷⁹ based in host community⁸⁰ ☐

6.1.3. acknowledgement of the right of regulatory body based in host community to discontinue trial ☐

6.2. Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate ___/4

6.2.1. trial registered with an international trial registry⁸¹ ☐

6.2.2. funding source(s)/ in-kind support disclosed ☐

6.2.3. mentioned reference to/use of bioethics guidelines developed by each host country ☐

6.2.4. mention of international consultation or use of international guidelines⁸² ☐

6.3. Ensure independence and competence of the reviews ___/3

6.3.1. specification of measures taken to ensure independence and competence of ethics review⁸³ ☐

6.3.2. specification of measures taken to prevent situations of conflict(s) of interest⁸⁴ ☐

6.3.3. strategy to assist local ethics committee in reaching international standard procedures⁸⁵

⁷⁵ IOM R9-8

⁷⁶ i.e., both benefits and risks are fully listed; measures taken to maximize benefits and measures taken to minimize risks are described. **UNAIDS GP12** *Extraneous benefits, such as payment or ancillary services, such as HIV risk-reduction interventions or reproductive health care services, should not be considered in the risk-benefit analysis.*

⁷⁷ Check items in this section if references are named. E.g., The National Agency for Food and Drug Administration and Control (NAFDAC) –not a vague statement as “the relevant regulatory body in Nigeria”.

⁷⁸ **UNAIDS GP10** *Survey of applicable local laws is an essential requirement.* If it is an multi-country trial, this should be specified for each site.

⁷⁹ This can be identified as Institutional Review Board (IRB), Review Ethics Board (REB), etc

⁸⁰ **UNAIDS GP4** *Proposed biomedical HIV prevention trial protocols should be reviewed by scientific and ethical review committees that are located in, and include membership from, the country in which researchers wish to operate.*

⁸¹ **UNAIDS GP4** *Trials should register with an international trial registry prior to committee review as a condition of approval.*

⁸² **UNAIDS GP4** *Capacity-building in scientific and ethical review may also be developed in collaboration with international agencies, organisations within the host country, and other relevant parties. E.g., UNESCO Ethics Observatory.*

⁸³ **UNAIDS GP4**

⁸⁴ **UNAIDS GP4** *Independent ethical review (...) minimizes concerns with regard to researchers' conflicts of interest because of relationships with the sponsors or pressures from those promoting the research.*

⁸⁵ **IOM R7-2** *If the regulatory infrastructure of a planned study site is insufficient, study sponsors, funding agencies, research organizations, and other stakeholders should assist local IRBs in developing the ability to provide comprehensive and timely oversight of clinical trials according to international standards. **UNAIDS GP4** Some countries do not currently have the capacity to conduct independent, competent, and meaningful scientific and ethical review. If the country's capacity for scientific and ethical review is judged to be inadequate, the sponsor should be responsible for ensuring that adequate structures for scientific and ethical review prior to the start of the research are developed in the country in which the trial will take place — or the research should not take place.*

7. INFORMED CONSENT (5 benchmarks)

/12 items

- 7.1. Involve the community in establishing recruitment procedures and incentives** ___/2
- 7.1.1. consultation with host community for appropriate recruitment procedures and compensation⁸⁶
- 7.1.2. recruitment method is explained and participants source(s)⁸⁷ is/are specified⁸⁸ ☐
- 7.2. Disclose accurate information in culturally and linguistically appropriate formats** ___/3
- 7.2.1. information available to participants/community in local official language(s)/main dialect(s)⁸⁹ ☐
- 7.2.2. information disclosed in plain language and clearly stating potential risks for study participants⁹⁰ ☐
- 7.2.3. information disclosed to participants/community in a culturally sensitive manner⁹¹ ☐
- 7.3. Implement supplementary community and familial consent procedures where culturally appropriate** ___/1
- 7.3.1. discussion on relevance of supplementary community and familial consent procedures⁹² ☐
- 7.4. Obtain consent in culturally and linguistically appropriate formats** ___/5
- 7.4.1. informed consent is an iterative process⁹³ ☐
- 7.4.2. time allowed to read consent form off-study site before signing⁹⁴ ☐
- 7.4.3. specific modalities for conduct and documentation of consent process for illiterate participants ☐
- 7.4.4. oral explanations given and opportunities to ask questions offered⁹⁵ ☐
- 7.4.5. systematic measures to assess comprehension of disclosed information by potential participant⁹⁶ ☐
- 7.5. Ensure the freedom to refuse or withdraw** ___/1
- 7.5.1. description of measures to prevent/address coercion⁹⁷ ☐

8. RESPECT FOR RECRUITED PARTICIPANTS AND STUDY COMMUNITIES (5 benchmarks)

/09 items

⁸⁶ **IOM R6-1** Investigators should conduct pretrial research to assess the community and individuals' interest in the trial, to pilot test recruitment and retention strategies, and to set a realistic timeline and resource needs for the enrollment period and for retention.

⁸⁷ i.e., source(s) from which participants are recruited is/are mentioned (e.g., health center, community association, geographical area).

⁸⁸ **UNAIDS GP7** Selection and recruitment of communities and individuals for participation in a trial must be fair and should create a research climate which shows respect for all persons.

⁸⁹ **UNAIDS GP16** The information should be presented in appropriate forms and languages, including written information sheets.

⁹⁰ **UNAIDS GP16** This includes clearly stating that product is experimental and it is not known that it will prevent HIV infection or disease.

⁹¹ **UNAIDS GP8** Sensitivity to factors of potential vulnerability, including language and cultural barriers, should inform procedures for recruiting and screening potential participants, informed consent processes, and the support, care, and treatment that participants receive in relation to the trial.

⁹² **UNAIDS GP7, GP10**

⁹³ **UNAIDS GP16** Biomedical HIV prevention trials require informed consent for all components of participation at a number of stages. (...) Consent should be sought for interviews on personal matters, medical tests (including HIV test), physical examinations, etc

⁹⁴ **UNAIDS GP16** Time should be allowed to consider participation, discuss with others such as partners, and ask questions.

⁹⁵ **UNAIDS GP16** There should be oral communication of information, especially for participants who may be illiterate.

⁹⁶ **UNAIDS GP16** Throughout all stages of the trial and consent process, there should be assurance by the investigator that the information is understood by the participant before consent is given. (...) In addition, there should be oral communication of information, especially for participants who may be illiterate and standardized tests for assessment of comprehension, where necessary.

⁹⁷ **UNAIDS GP16 Special Measures** This includes persons who are junior or subordinate members of hierarchical structures (...), persons who engage in illegal or socially stigmatised activities (...), persons who are impoverished or dependent on welfare programmes. This also may concern women, as voluntariness of participation may also be compromised where there is a cultural tradition of men holding decision making authority in marital relationships, parental control of women, and other forms of social subjugation and coercion.

- 8.1. Develop and implement procedures to protect the confidentiality of recruited and enrolled participants** ___/1
- 8.1.1. specification of procedures to protect confidentiality of recruited and enrolled participants⁹⁸ ☐
- 8.2. Ensure that participants know they can withdraw without penalty** ___/1
- 8.2.1. systematic steps to insure that enrolled participants know their rights regarding withdrawing⁹⁹ ☐
- 8.3. Provide enrolled participants with information that arises in the course of the research study** ___/2
- 8.3.1. statement about updating information disclosed to participants with relevant new information¹⁰⁰ ☐
- 8.3.2. consent to be confirmed in cases that may affect participant's willingness to remain involved¹⁰¹ ☐
- 8.4. Monitor and develop interventions for medical conditions including research-related injuries, for enrolled participants at least as good as existing local norms** ___/4
- 8.4.1. description of relevant local health care standards in each study site¹⁰² ☐
- 8.4.2. description of health monitoring/care plan for study participants during trial period¹⁰³ ☐
- 8.4.3. discussion about appointing ombudsperson or partnering with independent organization¹⁰⁴ ☐
- 8.4.4. compensation plan for trial-related harm¹⁰⁵ ☐
- 8.5. Inform participants and the study community of the results of the research** ___/1
- 8.5.1. statement about giving feedback to participants/host community about study results¹⁰⁶ ☐

⁹⁸ **UNAIDS GP18** Researchers have an ongoing obligation to participants to develop and implement procedures to maintain the confidentiality and security of information collected.

⁹⁹ **UNAIDS GP17** Special attention should be given to ensure that individuals are aware of their right to withdraw from a trial without any penalty, and that they are actually free to do so.

¹⁰⁰ e.g., new data from concurrent study, decision from regulatory body that affects trial.

¹⁰¹ This includes protocol amendments (e.g., prolonged duration of follow-up) and changes in participants' medical status.

¹⁰² This is particularly relevant if study is conducted internationally, and should include basic medical care, reproductive care, psychological care, social support, social services, and HIV management (including treatment with antiretrovirals). **UNAIDS GP3** Factors that affect perceptions of disparity in power between sponsors and the countries and communities in which research takes place may include (...) local infrastructure, personnel, and technical capacity for providing comprehensive HIV health care and treatment options; (...) local infrastructure, personnel, and laboratory and technical capacity for conducting the proposed research.

¹⁰³ **UNAIDS GP12** This should be a description of what is covered by the research team and where participants should go for care of other health issues.

¹⁰⁴ **UNAIDS GP11** To intervene on behalf of participants with outside parties, if necessary and requested. **UNAIDS GP13** Consideration should be given to providing counselling through an agency or organisation that is independent of the investigators in order to prevent any real or perceived conflict of interest.

¹⁰⁵ **UNAIDS GP11** Both the protocol and the informed consent process should describe the nature of medical treatment to be provided for injuries, as well as compensation for harm incurred due to research-related activities and the process by which it will be decided whether an injury will be compensated. HIV infection acquired during participation in a biomedical HIV prevention trial should not be considered a compensable injury unless directly attributable to the prevention product being tested itself, or to direct contamination through a research-related activity.

¹⁰⁶ **UNAIDS GP19** Researchers should inform trial participants and their communities of the trial results.

ATTACHMENT 4

Consent Content Analysis Form

【附注】(1) 本表根据《中国统计年鉴》(2006) 数据整理。(2) 本表根据《中国统计年鉴》(2006) 数据整理。(3) 本表根据《中国统计年鉴》(2006) 数据整理。

[illegible]

1. IDENTIFICATION OF SELECTED TRIAL

www.elsevier.com/locate/jmb
doi:10.1016/j.jmb.2006.05.011

NCT ☐ no

2. CONSENT FORM DESCRIPTION

2.1. Presentation of consent form

1

☐

2.2. Type(s) of consent form(s) mentioned

1

3. CONSENT FORM READABILITY (*Microsoft Word function*)

3.1. Counts

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3.2. Averages**3.2.1. Sentences/paragraph**

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3.2.2. Words/sentence

— —'—

3.2.3. Characters/word

— —'—

3.3. Readability**3.3.1. Passive sentences**

— — %

3.3.2. Flesch Reading Ease

— —'—

3.3.3. Flesch-Kincaid Grade Level

— —'—

4. CONSENT FORM CONTENT**4.1. UNAIDS Guidance Point 16****4.1.1. reasons justifying choice of prospective participants^a**☐**4.1.2. experimental nature of the biomedical HIV prevention product**☐**4.1.3. uncertainty regarding effectiveness of product in preventing HIV infection or disease**☐**4.1.4. use of a placebo instead of HIV prevention test-product in randomly selected participants**☐**4.1.5. provision of counselling concerning risk reduction of HIV exposure**☐**4.1.6. access to risk-reduction means^b**☐**4.1.7. possibility that, in spite of risk-reduction efforts, some participants may become infected^c**☐**4.1.8. specific risks for physical harm**☐**4.1.9. specific risks for psychological and social harm^d**☐**4.1.10. types of treatment and compensation that are available for harm**☐**4.1.11. potential referral services should harm occur**☐**4.1.12. nature and duration of available care and treatment**☐**4.1.13. means to access available care and treatment, if HIV seroconversions occurs during trial^e**☐**4.1.14. collection, use, and period of storage of participants' biological samples and specimens**☐**4.1.15. options for disposal of samples and specimens at the conclusion of the trial^f**☐**4.1.16. use, confidentiality, period of storage, and disposal of personal data^g**☐**4.1.17. option to refuse to allow use of personal data beyond scope of the specific trial^h**☐^a including whether they are at higher risk of HIV exposure^b in particular, male and female condoms, clean injecting equipment, and where relevant, male circumcision^c particularly in the case of phase III trials where large numbers of participants at higher risk of HIV exposure are participating^d see Guidance Point 11^e see Guidance Point 14^f including the option to refuse to allow use of such samples or specimens beyond the scope of the specific trial^g including genetic information^h see Guidance Point 18



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