



Javier R. Lama, MD, MPH

**Asociación Civil
Impacta Salud y Educación**
Av. Grimaldo del Solar 805
Lima 18, Perú
t. + 51.1.242.3072
f. + 51.1.242.2467
jrlama@impactaperu.org
www.impactaperu.org



Robert M. Grant, MD, MPH

**Gladstone Institute of
Virology and Immunology**
and
**University of California,
San Francisco**
1650 Owens Street
San Francisco
California 94158, USA
t. + 1.415.734.4810
f. + 1.415.552.5980
rgrant@itsa.ucsf.edu
www.gladstone.ucsf.edu



Martín Casapía, MD

**Asociación Civil
Selva Amazónica**
Urb. Jardín No. 27
Iquitos, Maynas, Perú
t. + 51.65.23.6277
f. + 51.65.22.1827
mcasapia@impactaperu.org
www.impactaperu.org

Research on Chemoprophylaxis for HIV Prevention in Men

February 21, 2006

Julie Davids
Executive Director
CHAMP
Email: Jdavids@champnetwork.org
Telephone 646-431-7525

Dear Julie,

We are writing in response to "A Statement of Support for HIV Prevention Research on Pre-Exposure Prophylaxis" which was circulated on February 7th, 2006. We appreciate your enthusiasm for research on novel approaches to HIV/AIDS prevention, including use of potent and generally well-tolerated antiviral agents for prevention of infection. *We heartily agree that "we must swiftly and ethically answer the question: Does PrEP work and is it safe?"*

In your statement, you request an update for the community which addresses:

- the statistical power of the current trials to answer questions about safety and efficacy in various populations and with respect to various modes of transmission,
- plans for future trials if preliminary data suggest efficacy,
- status of regulatory discussions about how the product would be labeled if it proved effective against one mode of transmission or in one population.

The following information is provided in the spirit of open communication, and to inform interested communities about the progress of this important area of research. The success of this research depends on the support of fully informed communities who provide advice, advocacy, and participation.

The information provided here is the best available to us as of this date. The undersigned take responsibility for the views presented here, which may not reflect the views of other individuals and institutions involved in the PrEP research field.

Sincerely,

Robert M Grant, MD, MPH
Principal Investigator, "Chemoprophylaxis for HIV Prevention in Men"
Associate Investigator, Gladstone Institute of Virology and Immunology
Associate Professor of Medicine, University of California, San Francisco.

David Glidden, PhD
Statistician, "Chemoprophylaxis for HIV Prevention in Men"
Associate Professor of Statistics, University of California, San Francisco

First Question: What is the statistical power of the current trials to answer questions about safety and efficacy in various populations and with respect to various modes of transmission?

Note on study designs:

As with most scientific research, there is no over-arching authority that governs the field of chemoprophylaxis research. There are more than 30 PrEP investigators who come from ten different countries. There are multiple sponsors, including the US National Institutes of Health, Family Health International, and the Centers for Disease Control. The Bill and Melinda Gates Foundation provides funding to Family Health International. Gilead Sciences provides drug and placebo for all the trials, but is not providing funding. Regulations and ethical norms that govern research in the countries of the sponsors and investigators apply to PrEP research projects.

Despite their diverse origins, the PrEP study protocols have several characteristics in common:

- 1) Randomized assignment to active drug and placebo
- 2) Randomization ratio of 1:1 (active:placebo)
- 3) Blinding such that neither the participant nor the investigators know whether the participant is receiving active drug or placebo
- 4) Frequent follow-up for HIV seroconversion and safety

**CLINICAL TRIALS OF PRE-EXPOSURE PROPHYLAXIS
USING TENOFOVIR-CONTAINING REGIMENS**

<i>Spon- sor</i>	<i>Location</i>	<i>Target Population</i>	<i>Primary Type Of exposure</i>	<i>N Planned</i>	<i>Ave. Months On Study Drug</i>	<i>Status</i>	<i>Expected Completion</i>
NIH/ FHI	Cambodia	Women	Vaginal	960	12	Stopped before starting	n/a
FHI	Ghana	Women	Vaginal	400	12	Enrolled	2006
FHI	Nigeria	Women	Vaginal	400	12	Stopped after enrolling ~130	2006
FHI	Cameroon	Women	Vaginal	400	12	Stopped after enrolling 400	2006
FHI	Malawi	Heterosexual Men	Penile	400	12	Stopped before starting	n/a
CDC	Thailand	IDU	Parenteral	1200	12	Enrolling	2008
CDC	Botswana	Heterosexual Men and Women	Vaginal/ Penile	1600	18	Enrolling	2008
CDC	SF/Atlanta	MSM	Penile/ Rectal	400	15	Enrolling	2008
NIH	Peru	MSM	Penile/ Rectal	1400	18	Planning	2009

Note on statistical power and sample size:

The clinical trials are designed to have power to answer important questions about the safety and efficacy of pre-exposure prophylaxis in specific populations. "Power" is defined as the chance of detecting a desired level of efficacy and safety.

The following discussion focuses on the power to detect efficacy, or the percentage decline in the risk of acquiring HIV among those who are given pre-exposure prophylaxis in addition to counseling, condoms and other standard prevention interventions. Power to detect efficacy depends on a large number of factors including:

- 1) The number of persons in the study (the sample size)
- 2) The duration of follow-up on study drug
- 3) The incidence of HIV in placebo group
- 4) The desired level of efficacy
- 5) The percentage of persons who are lost to follow-up
- 6) The level of statistical significance desired (usually 0.05)
- 7) Whether we are only interested in decreases in risk, or whether increases in risk would be important as well (ie: two-tailed or one-tailed testing; usually two tailed).

The level of desired efficacy is an important aspect of this consideration. The target efficacy level is different for every intervention. For example, HIV counseling and testing is important even when it decreases HIV risk by less than 35 percent. Vaccine trials frequently aim to detect 35% efficacy because a vaccine could be relatively inexpensive and easy to implement widely. Trials of daily oral chemoprophylaxis have been designed to detect higher levels of efficacy (60 to 90%) because we believe that these interventions would be definitely useful if they are highly effective. The higher standard for efficacy used in chemoprophylaxis research is based on the costs of PrEP program implementation, including the need for laboratory monitoring. High levels of efficacy have been observed when chemoprophylaxis is used to prevent malaria infection in travelers and tuberculosis pneumonia in those recently exposed to tuberculosis cases. In both of these situations, we believe that chemoprophylaxis has approximately 80 to 90 percent efficacy. The efficacy of oral contraception to prevent unwanted pregnancy is over 99 percent.

The calculations in the following tables were performed based on the following assumptions:

1. The level of HIV incidence indicated in the title of the table, ranging from 2% to 4%.
2. The desired level of efficacy to be detected ranging from 80% to 90%.
3. The planned sample size and study duration.
4. 10% loss to follow-up during the study
5. Two-tailed statistical tests
6. Acceptable statistical significance of 0.05.

The calculations were performed by simulation so there is some random variation in the estimates of power. Simulations were evaluated using likelihood ratio tests.

The power calculations are based on widely available information about the studies and consistent application of assumptions and methods. These estimates do not take into account site-specific information regarding expected retention rates or incidence rates, which are often

unavailable or unreliable because prior experience does not apply equally to each trial. The power estimates reflect the opinion of the undersigned, and do not necessarily reflect the views of the study investigators involved in each study.

Assumes 4% placebo incidence, 90% target efficacy

<i>Risk Group</i>	<i>No. Participants projected</i>	<i>Expected Person Years of Observation</i>	<i>Power</i>	<i>95% Confidence Interval of efficacy estimate</i>
MSM				
Peru	1400	1890	100%	71% to 97%
SF/ATL	<u>400</u>	<u>585</u>	<u>93%</u>	<u>26% to 98%</u>
MSM Total	1800	2445	100%	76% to 96%
Heterosexual Women				
Botswana	800	1080	100%	57% to 97%
Ghana	<u>400</u>	<u>360</u>	<u>79%</u>	<u>0 to 98%</u>
Heterosexual Women Total	1720	1700	100%	66% to 97%
Heterosexual Men	800	1080	99%	57% to 97%
Injection Drug Users	1200	1080	100%	57% to 97%

Assumes 4% placebo incidence, 80% target efficacy

<i>Risk Group</i>	<i>No. Participants projected</i>	<i>Expected Person Years of Observation</i>	<i>Power</i>	<i>95% Confidence Interval of efficacy estimate</i>
MSM				
Peru	1400	1890	100%	57% to 91%
SF/ATL	<u>400</u>	<u>585</u>	<u>79%</u>	<u>12% to 95%</u>
MSM Total	1800	2445	100%	61% to 90%
Heterosexual Women				
Botswana	800	1080	96%	44% to 93%
Ghana	<u>400</u>	<u>360</u>	<u>61%</u>	<u>0 to 96%</u>
Heterosexual Women Total	1720	1700	99%	52% to 92%
Heterosexual Men	800	1080	96%	45% to 93%
Injection Drug Users	1200	1080	96%	45% to 93%

Assumes 2% placebo incidence, 90% target efficacy

<i>Risk Group</i>	<i>No. Participants projected</i>	<i>Expected Person Years of Observation</i>	<i>Power</i>	<i>95% Confidence Interval of efficacy estimate</i>
MSM				
Peru	1400	1890	99%	52% to 97%
SF/ATL	<u>400</u>	<u>585</u>	<u>71%</u>	<u>0% to 98%</u>
MSM Total	1800	2445	100%	63% to 97%
Heterosexual Women				
Botswana	800	1080	92%	19% to 98%
Ghana	<u>400</u>	<u>360</u>	<u>54%</u>	<u>0 to 96%</u>
Heterosexual Women Total	1720	1700	96%	37% to 97%
Heterosexual Men	800	1080	91%	18% to 98%
Injection Drug Users	1200	1080	91%	22% to 98%

Summary of Power Calculations:

If planned and enrolling trials completely enroll, the existing international portfolio of PrEP research is sufficiently powered to detect high levels of efficacy (80 to 90%) in high risk groups of each of four populations (MSW, WSM, IDU, and MSM).

The trials may fail to demonstrate efficacy if the incidence of HIV in the study populations proves to be lower than 2%. This could occur if the highest risk groups are not identified because of social stigma or logistical reasons, or if they are preferentially lost to follow-up. In addition, provision of standard prevention interventions in these populations is expected to decrease incidence, although incidence levels above 2 percent are typically observed despite intensive counseling and condom promotion (eg: Explore study in the United States).

The studies will also obtain information about safety, including assessments of renal function, liver health, bone mineral density, drug resistance, viral load and CD4 T cell counts after seroconversion, antiviral immune responses, adherence patterns, drug levels, and interactions with hepatitis B viruses.

Studies are also assessing risk behavior and sexually transmitted infections to determine if risk behavior increases or decreases during PrEP research. Some people have raised the concern that biomedical prevention measures (like PrEP or vaccines) could increase risk behavior. This is an important concern, although risk behavior has been observed to *decrease* after post-exposure prophylaxis, likely reflecting the provision of counseling and condoms to all recipients. If PrEP efficacy and safety is confirmed, additional research will be warranted to optimize how best to convey PrEP recommendations, including best practices for counseling tailored for PrEP use.

Taken together, these studies will obtain information about the factors that are important in assessing the cost-effectiveness and acceptability of PrEP in HIV impacted populations.

Question 2: What are plans for future trials if preliminary data suggest efficacy?

Trials performed in West Africa may report information about safety and efficacy in women exposed to men as early as the 2nd quarter of 2006. This information will be limited due to trial closures in Nigeria and Cameroon. Nonetheless, valuable confirmation of safety and very preliminary information about efficacy in this one population may become available. The information from West Africa will not be sufficient to justify a general public health recommendation for PrEP, such that existing trials are expected to go ahead to collect additional information.

Larger studies in all risk groups are expected to begin reporting in 2008. See the following table which considers several possible outcomes of the research, and the implications for future research.

Possible Outcomes PrEP Trials and Next Steps

<i>Possible Outcome of Trials</i>	<i>Next Steps in PrEP research and utilization</i>
Efficacy in all populations with little or no drug resistance or toxicity.	Public health recommendations for PrEP for high risk persons would be developed by the US Centers for Disease Control, the WHO, and National Ministries of Health. These recommendations would be used to seek reimbursement by health care sponsors at the national and international levels. Future research would focus on optimal counseling strategies, optimal dosing intervals, operations research, use in young persons, and PrEP effects on immune responses induced by viral and vaccine exposures. If appropriate liability protections can be achieved (as they have for vaccines), the drug manufacturer may present data from studies performed under Good Clinical Practice and which meet international ethical standards to regulatory authorities to determine if a prevention indication can be added to the drug label. A prevention indication in the drug label may not be required for reimbursement and fund raising (for example HAART and NVP are used widely for MTCTP, but are not licensed for such). Active surveillance of PrEP utilization would be essential to characterize failures and monitor safety.
Efficacy in some populations, but not in all.	Public health recommendations for PrEP in high risk groups shown to benefit would be expected. Some utilization outside the groups shown to benefit will be expected, especially since restricting reimbursement based on HIV risk groups is not feasible. Additional research to identify the mechanisms accounting for different efficacy in different groups would be conducted using specimens preserved during the trials and animal models. Possible mechanisms for different efficacy may include differences in adherence, pharmacokinetics, drug penetration into exposed tissues, differences in mucosal biology, or different intensity of exposure. The design of further clinical PrEP research would depend on hypothesized explanations for PrEP failure that arise from the research. New research may be based on active monitoring of utilization in clinical practice, clinical trials of new agents, new adherence strategies, or new routes of drug administration. If there are trends toward efficacy in all risk groups, and demonstrated efficacy in at least one risk group, the drug manufacturer may present data from studies to regulatory authorities to add a prevention indication to the drug label. Active surveillance of PrEP utilization in each population group would be essential to characterize failures and monitor safety.
No evidence of efficacy	Current research may fail to detect efficacy if PrEP has efficacy that is less than 50%. If very high levels of safety are confirmed, and drug resistance proves not to be a problem, a second generation of larger trials designed to detect lower levels of efficacy (35% to 60% range) may be considered. Research into the mechanisms of PrEP failure would be conducted using specimens collected in the trials and from non-human primates. Possible mechanisms of failure include drug resistance, poor adherence, poor drug penetration into cell-types important for transmission, or lack of overall regimen antiviral activity. Efficacy studies of alternative regimens would be recommended if new agents or dosing mechanisms became available that address the limitations of the first generation of trials.
Low placebo-group incidence.	Low placebo group incidence will decrease power to detect efficacy. This may occur if sites are unable to identify high risk groups due to logistical reasons or if standard prevention methods prove to be unusually effective. Research would focus on methods for identifying and recruiting higher risk groups, and understanding how to replicate the prevention success of the trial. PrEP data from all studies would be analyzed together to increase power. If PrEP is found to be efficacious after pooling all data, this may lead to a recommendation for PrEP for high risk persons who cannot utilize standard methods. Active surveillance of PrEP utilization in each population group would be essential to characterize failures and monitor safety.
Poor tolerability or toxicity.	Future PrEP research may focus on dose reduction or different agents that were better tolerated.
Drug resistance occurs.	Future PrEP research would focus on regimens which contain a larger number of agents, higher potency, better tissue penetration, or higher viral fitness barriers to resistance. Research on topical dosing of PrEP is already in progress.

Question 3. What are the status of regulatory discussions about how the product would be labeled if it proved effective against one mode of transmission or in one population?

Regulatory discussions and product labeling are critical for the development of new agents (drugs or vaccines) that have not yet been licensed for any use (or “indication”). In the United States, new drugs or vaccines cannot be used in clinical practice unless they have been licensed or there is an IND (Investigational New Drug permit) by the FDA. The drug manufacturer usually sponsors and controls the research needed to obtain licensing, which is essential for future clinical use and business success. This type of drug or vaccine development is highly controlled by manufacturers and regulators, and the process is now familiar to sponsors, researchers, community representatives and activists.

The drugs used in PrEP trials are already licensed for HIV treatment. Research that seeks new uses for drugs that are already licensed creates very different regulatory discussions. Once licensed for any indication, drugs can be legally prescribed by any licensed physician for any use, as part of a research study or following an accepted practice standard. For example, a variety of antiviral drugs are currently used in the United States to prevent mother to child transmission, and after significant exposure to HIV from a needlestick. None of the drugs are currently labeled for these prevention uses, except zidovudine which is labeled for prevention of maternal to child transmission. Nonetheless, insurance payers and international funds routinely pay for the costs of post-exposure prophylaxis and maternal to child transmission prevention.

If information from PrEP trials are sufficient to establish a medical practice standard, the drugs can be used in the new way. Insurance providers and international funding agencies will evaluate the research and also look at cost-effectiveness and alternatives before deciding to reimburse the costs of PrEP. In anticipation of these information needs, all of the PrEP trials have been designed to collect high quality information in rigorously designed and implemented clinical trials. Also, policy and reimbursement implications are being analyzed and discussed.

The value of changing the drug label to include a prevention indication is mainly that it would permit the drug manufacturer to advertise the prevention use of the drug. The value of such advertising for the public’s health is unclear, given that PrEP is expected to become popularized if it is demonstrated to be highly safe and effective. The value of advertising for the drug manufacturer is also unclear, because it may not increase sales and could increase liability if anyone becomes infected despite using the drug in the manner that was advertised. Full scale promotion of PrEP by drug manufacturers may be helpful, but likely would require government protections from liability similar to those offered vaccine manufacturers.

PrEP research in Peru that is sponsored by the National Institutes of Health will be performed under an IND with the Food and Drug Administration. This is not a legal requirement. Other efficacy research performed outside of the United States can be presented to the FDA after the trial is completed if the data is of high quality and ethical standards have been met. It is acknowledged that trials will need to be completed in all major risk groups if a prevention indication can be added to the drug label.