A Systematic Review to Determine if Preexposure Chemoprophylaxis Reduces or Prevents HIV/AIDS Transmission

Holly Hawkins

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Abstract
Background: HIV/AIDS is one of the most destructive and lethal health crises of today's world. The stigma and resulting discrimination of HIV/AIDS is almost as deadly as the virus itself. Because a vaccine or cure does not exist, HIV/AIDS will continue to spread and therefore, prevention remains the key to curbing this epidemic. One method of combating this disease is through the administration of preexposure chemoprophylactic agents prior to the exposure of the infectious agent. For this systematic review, the evidence from two studies were evaluated using the GRADE tool.

Method: An exhaustive search of available medical literature was conducted using Medline, Web of Science, Cochrane Systematic Reviews, CINHAL, and EBM Multifile Review.

Results: Two randomized controlled trials were reviewed. Both studies showed a reduction in HIV/AIDS acquisition with the use of anti-retroviral preexposure prophylaxis.

Conclusion: The administration of anti-retroviral preexposure chemoprophylaxis decreases the transmission rate of infection. The GRADE for the evidence was high.

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HIV, Anti-Retroviral Agents, Prevention, and Tenofovir

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A Systematic Review to Determine if Preexposure Chemoprophylaxis Reduces or Prevents HIV/AIDS Transmission

Holly Hawkins

A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science

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Clinical Graduate Project Instructors: Torry Cobb, DHSc, MPH, PA-C & Annjanette Sommers MS, PA-C
Biography

Holly Hawkins is currently studying at Pacific University to achieve her Master of Science in Physician Assistant Studies. She was born and raised in rural Idaho. She completed her Bachelor of Science with a double minor in Addiction Studies and Psychology from Boise State University, in 2007.

When she isn’t engaged in professional or academic pursuits, she enjoys mountain and road biking, snowboarding, hiking, and spending time with family, friends and her dog Riley.

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To my family and close friends, thank you for your unconditional love, continued support, encouragement and belief in me. It has allowed for personal growth, development and achievement that would have otherwise been unattainable.
ABSTRACT

Background: HIV/AIDS is one of the most destructive and lethal health crises of today’s world. The stigma and resulting discrimination of HIV/AIDS is almost as deadly as the virus itself. Because a vaccine or cure does not exist, HIV/AIDS will continue to spread and therefore, prevention remains the key to curbing this epidemic. One method of combating this disease is through the administration of preexposure chemoprophylactic agents prior to the exposure of the infectious agent. For this systematic review, the evidence from two studies were evaluated using the GRADE tool.

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INTRODUCTION

Background

The Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is one of the most destructive and lethal health crises in today’s world. This major health emergency has continued to ravage families and communities across the globe for nearly thirty years despite the continued efforts to develop an effective vaccine. The armamentarium for preventing the transmission of HIV/AIDS and decreasing the impact of this deadly disease are continuing to slowly propagate. Although its exact origins are uncertain, it is largely believed HIV/AIDS came about through the interaction of humans with other species, likely as a result from apes being hunted, butchered, or eaten (New Yorker, 2010). According to AVERT (2010), an international HIV/AIDS charity, an estimated 33.3 million people worldwide were living with HIV/AIDS in 2009, with women accounting for just over half of all adult cases. AVERT (2010) also published that 1.8 million HIV/AIDS deaths were reported in the same year. Every day, more than 7,000 people are newly infected around the globe with HIV/AIDS (AVERT, 2010). This pandemic continues to spread globally in spite of the many prevention efforts.

Discrimination, social unrest, maltreatment and abuse are a few problems that undermine the human rights of those who are HIV/AIDS positive (World Health Organization [WHO], 2006). The stigma and resulting discrimination of HIV/AIDS along side misogyny which leads to homosexual and heterosexual behaviors continues to impact the spread of the virus. HIV/AIDS continues to be
a barrier to public action while also remaining a social issue which people are reluctant to address. In continents such as Africa, that have been heavily impacted by the HIV/AIDS epidemic, the losses of individuals and productive citizens have not only affected family units but have also affected workplaces, schools, health systems and governments (Ashford, 2006). According to Ashford (2006), this epidemic has touched every single facet of the living. Because a vaccine or cure does not exist, HIV/AIDS will continue to spread and therefore, prevention remains the key to curbing this pandemic.

The only known way for HIV/AIDS transmission to take place is through direct contact with the blood or bodily fluids (semen, vaginal fluid, preseminal fluid and breast milk) of someone who is infected with the virus (AVERT, 2011). Like other viruses, HIV/AIDS can only sustain life in living organisms. The most common ways in which HIV/AIDS is propagating throughout the world is through contact between sexual secretions of one person with the genital, rectal or oral mucosa membranes of another person, sharing injection paraphernalia to transfuse blood, inject drugs or other substances, and by transmission from infected mothers to their newborns during pregnancy, labor, or breastfeeding (AVERT, 2011). Although the risk of HIV/AIDS contagion is very low through casual exposure, it is still theoretically possible. Antibody testing remains the best method for diagnosis.

Prevention of HIV/AIDS is the key to eliminating this deadly virus. Current practices that have been shown to decrease the transmission of HIV/AIDS are abstinence, delaying the age at which young people first engage in sexual
intercourse, monogamy, education, condom promotion and use, improved access to condoms, male circumcision, substance addiction therapy, treatment of sexually transmitted infections and HIV/AIDS testing and counseling (WHO, 2006). A recent study conducted in Africa performed by Peterson et al. (2007) demonstrated with proper education people will change their sexual behavior. In this study, self reported condom use increased from 52 percent at screening to approximately 92 percent during the follow up period (Peterson et al., 2007). The conjecture in this increased condom use reflects the services that were provided such as HIV/AIDS testing and counseling services and the dispensing of condoms (Peterson et al., 2007). Youth are at the core of the global HIV/AIDS epidemic, both in terms of new infections and in opportunities for halting the transmission (WHO, 2006). Providing youth with HIV/AIDS education is vital and can only help to contain the current population infected, and protect against future spread. The most recent dramatic success in prevention has been the reduction of mother to child transmission through the use of anti-retroviral (ARV) chemotherapeutics. This development has led many recent trials and investigations to take a closer look at preexposure chemoprophylaxis (PrEP) therapy with the use of ARVs by HIV/AIDS negative individuals to reduce their overall risk of acquiring the virus. The use of ARV therapy for prevention of HIV/AIDS can lead to suppression of viral replication in the bloodstream and in genital tract secretions, which then would decrease transmission of this deadly disease (El-Sadr, 2010).
One such ARV is tenofovir, which is an anadenosine nucleotide analogue belonging to a class of antiviral medications that is called reverse transcriptase inhibitors (National Center for Biotechnology Information [NCBI], 2010b). Tenofovir has potent activity against retroviruses and works by slowing the spread of HIV/AIDS in the body (NCBI, 2010b). It was initially developed and tested as a prophylactic ARV drug on monkeys and was subsequently formulated for oral use to treat HIV/AIDS in humans (NCBI, 2010b). When used in conjunction with tenofovir and other drugs, emtricitabine is another ARV used to treat HIV/AIDS. Emtricitabine also works by slowing the spread of HIV/AIDS in the body by inhibiting reverse transcriptase, the enzyme that copies HIV/AIDS RNA into new viral DNA (NCBI, 2010a). Emtricitabine can help to lower the amount of HIV/AIDS, also known as the "viral load" in a patient's body by indirectly increasing the number of immune system cells overall which decreases the likelihood of acquiring the infection (NCBI, 2010a). Scientific evidence increasingly supports the view that ARV therapy is effective in reducing the risk of HIV/AIDS transmission by sustained suppression of the virus. In the same fashion ARV therapy can also impact couples with a discordant serostatus by lowering transmission (WHO, 2009). Prevention of mother to child transmission through the use of ARVs is proof of this concept. These pharmacological agents control the infection but do not cure it (NCBI, 2010). There are a number of biomedical technologies under development that show promise for preventing the spread of HIV/AIDS, unfortunately it may take years for these interventions to come to fruition.
Purpose of the Study

There is no cure for HIV/AIDS. Because of this, any strategies that will prevent the spread of the disease or the use of any medications that will decrease transmission of the disease are an important avenue to investigate. Several studies have suggested that PrEP is efficacious in preventing HIV/AIDS, however, insufficient research has been performed to date. The objective of this paper is to perform a systematic review of the literature on the use of ARV PrEP in high risk adults to determine if it will prevent or reduce the transmission of HIV/AIDS. In order to provide an objective evaluation, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group has been used (Guyatt et al., 2008).

METHODS

An extensive literature search was performed using Medline, Web of Science, Cochrane Systematic Reviews, CINHAL, and Evidence-Based Medicine Reviews Multifile. These databases were accessed through the Pacific University Library system. The keywords searched included “HIV”, “Anti-Retroviral Agents”, “Prevention”, and “Tenofovir” individually and in combination. The search was limited to human subjects, the English language and full text articles. The initial results included 16 articles. Articles published before 2000 were excluded. Only randomized, controlled trials were located which resulted in two studies that were directly related to the topic being reviewed. One study was conducted in South Africa and the other study was conducted multi-nationally.

RESULTS
The first study reviewed was performed by Grant et al., (2010) and appeared in the New England Journal of Medicine. The purpose of this study was to evaluate the safety and efficacy of oral emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) combination therapy (FTC-TDF) in a single tablet as compared to placebo for the prevention of HIV/AIDS. This study enrolled 2,499 participants at eleven sites in six countries: Peru, Ecuador, South Africa, Brazil, Thailand, and the United States. Inclusion criteria were male sex at birth, an age of eighteen years or older, HIV seronegative status and evidence of high risk for acquisition of HIV/AIDS infection (Grant et al., 2010). Each four-week visit included medical histories, drug dispensing, pill counts, adherence counseling, and rapid testing for HIV antibodies. The interviewer assessed high risk behavior every twelve weeks. Physical examination and evaluation for sexually transmitted infections was performed every 24 weeks. HIV/AIDS rapid testing was performed at 39,613 visits. New or emergent HIV/AIDS sero-conversion was observed in 100 patients. Among those 100 patients, 36 of them were in the FDC-TDF group and 64 of them were in the placebo group. This represented a 44 percent reduction in the new HIV/AIDS cases. The rate of compliance was 50 percent and was consistent across both the experimental and the placebo group. Furthermore, after discontinuation of the study drug, seroconversion rates were similar among the study groups. Drug levels were drawn, and of those with a detectable level, the odds of HIV/AIDS infection were lower by a factor of 12.9, corresponding to a relative reduction rate of HIV/AIDS of 92 percent. No FDC or
TDF resistance was detected during the study. Detectable blood levels strongly correlated with the prophylactic effect.

The side effects from FTC-TDF were mild and sparse. The most common side effect reported were nausea and unintentional weight loss of greater than five percent. Both were reported more frequently in the FTC-TDF group than the placebo group. No FTC or TDF resistance occurred in any of the participants who became infected with HIV/AIDS during the trial. A mild increase in creatinine levels suggestive of renal impairment were observed in the FTC-TDF group but were self limiting and were not confirmed on specific repeat testing (Grant et al., 2010). Self reported HIV/AIDS sexual risk behavior decreased in both arms of the study. The authors concluded that PrEP of FTC-TDF in high risk adult populations is effective in slowing the spread of HIV/AIDS (Grant et al., 2010).

The second study reviewed was conducted by The AIDS Program of Research in South Africa (CAPRISA) by Karim et al., (2010). The purpose of this study was to assess the effectiveness and safety of tenofovir gel for the prevention of HIV/AIDS infections in women vaginally. The authors enrolled 889 participants in the analysis. HIV/AIDS negative women from eighteen to forty years old who were sexually active (defined as having sex at least twice in the 30 days before screening), not pregnant, and using a nonbarrier form of contraceptive were eligible for enrollment (Karim et al., 2010). Women were requested to insert one dose of tenofovir gel into their vagina within twelve hours before sex and a second dose of gel as soon as possible but within twelve hours
after sex. No more than two doses of gel in a 24-hour period were to be used
(Karim et al., 2010). Each participant had monthly HIV/AIDS and urine
pregnancy testing performed before gel was dispensed. Compliance was
measured by self report. Drug safety was assessed at every study visit.
Participants underwent quarterly pelvic examinations, and if needed, colposcopy
(Karim et al., 2010). HIV/AIDS incidence rate in the tenofovir gel arm when
compared with the placebo gel arm, was 50 percent lower after twelve months of
follow up and 40 percent lower after 24 months of follow up (Karim et al., 2010).
In terms of assessing the effectiveness of the gel in preventing HIV/AIDS
infection, 98 HIV/AIDS infections occurred throughout the study, 38 in the
tenofovir gel arm and 60 in the placebo arm yielding an incidence rate ratio of
0.61. It reduced HIV/AIDS acquisition by an estimated 39 percent overall, and by
54 percent in women with high level of gel adherence (Karim et al., 2010). The
hazard ratio was 0.63 after adjusting for baseline co-variants (age, site, anal sex
history, contraceptive method, HSV-2 antibody status, and condom use). The
adherence estimates based on applicators returned indicated 72.2 percent of sex
acts were covered by two doses of gel (Karim et al., 2010). HIV/AIDS incidence
was directly correlated to the number of doses utilized. The participants with a
high level of adherence were 54 percent less likely to become infected with the
virus whereas the less adherent participants were 38 percent less likely to
become infected (Karim et al., 2010). The number of sex acts were indirectly
proportional to the quantity of gel utilized. Adherence was found to be higher in
women who did not acquire HIV/AIDS. The gel provided a 51 percent protective
effect against herpes simplex virus type 2 infection (Karim et al., 2010). There were no tenofovir resistance or resistant mutations detected in the tenofovir or the placebo arm. More diarrhea and gastrointestinal infections were reported among the participants using the tenofovir gel, but otherwise adverse events and other safety markers were very similar between the two study arms. No safety concerns were identified in the 22 women exposed to tenofovir gel in early pregnancy. No congenital abnormalities were seen in the babies born during the study. TDF has been shown to cause decreases in renal function. Whether this serves as a confounder of renal impairment, this will remain unknown because women with renal impairment were excluded from the CAPRISA study. Liver side effects or increases in heptic flares were not seen during the study, possibly because of the low systemic absorption of the tenofovir gel epicutaneously. The authors concluded that when tenofovir gel was used coitally, it appeared safe and effective in preventing HIV/AIDS infection (Karim et al., 2010).

DISCUSSION

General

The results of the CAPRISA trial, released in July 2010, showed that one percent tenofovir gel reduced the risk of HIV/AIDS infection in women by 39 percent compared with placebo, and increased incrementally as the women were more consistent with gel use (Karim et al., 2010). In some cases this was as high as 54 percent. This was the first clinical trial in almost twenty years to show
that a vaginal microbicide could provide a safe and effective way to prevent sexual transmission of HIV/AIDS. Interestingly the gel also provided a protective effect against herpes simplex virus type 2 infection (Karim et al., 2010).

In the Preexposure Chemoprophylaxis for HIV in Men Who Have Sex With Men (iPrEx) study, the arm that received ARV PrEP experienced an average of 44 percent fewer HIV/AIDS infections than the arm that received placebo (Grant et al., 2010). The authors reported 36 infections in the patients receiving FTC-TDF and there were 64 infections in participants receiving placebo (Grant et al., 2010).

Limitations

There were a number of study limitations observed in both studies reviewed. The study by Grant et al. (2010) had a recall bias because the subjects were interviewed every 12 weeks to review their sexual risk behavior. Reported high risk behavior substantially decreased after enrollment and remained lower than at baseline during the trial (Grant et al., 2010). A similar study in Western Africa showed a safer behavior in a trial of PrEP with TDF (Peterson et al., 2007). It is hypothesized that this may reflect the services that were provided such as HIV/AIDS testing and counseling services and the dispensing of condoms (Peterson et al., 2007). Furthermore, taking a pill may serve as a daily reminder of the risks one is undertaking, possibly leading to changes in sexual behavior overall reducing one’s risk of acquiring HIV/AIDS. Gel does not serve as a behavioral reminder because typically the decision has already been made to have sex when the gel is being used. Gel use is not
blinded to the study participant’s partner, therefore, it may alter the practices of
the sexual encounter. The cultural mores in different locations where studies
were conducted would play a large role in determining the final results if the sites
in Africa for example, might demonstrate the lack of autonomy of African women
in making sexual decisions for themselves as compared to those in the United
States. If individuals taking ARV PrEP feel protected against infection and
consequently increase their risky behavior, risk compensation will likely occur
(Supervie, 2010). Risk compensation is when individual people may tend to
adjust their behavior in response to perceived changes in risk. This could
potentially escalate the transmitted resistance. For example, the male may be
willing to take more risks because of the mindset that one’s partner is “protected”
when the gel is being used. It also may alter the type of sex that is being had
and may change the sensation or frequency of encounters due to changing the
experience of sex either in a positive or negative manner, i.e. better sensation
through decreased friction. The sexual act may become more pleasurable with
the use of gel for the woman if she suffers from vaginal dryness, therefore, she
might become more willing to participate in riskier sexual encounters. The pill
consumption is unknown to the sexual partner and therefore, not subject to any
behavior modifications based on knowledge of its use. Another limitation of this
study is the heterogeneity of the sexual practices being performed i.e.
heterosexual women and bisexual men (Grant et al., 2010). It is not known
whether the gel protects against the rectal transmission of HIV/AIDS thus
providing study participants with gel may actually serve to increase their
HIV/AIDS transmission rate, i.e. risk compensation, through the facilitation of high risk behavior.

Limitations were also present in the CAPRISA trial (Karim et al., 2010). This study also has a recall bias because it asks participants to self-report sex acts in the last 30 days and the adherence to the use of gel. Both are likely to be skewed by recall bias. Participants undoubtedly under report their sexual acts/encounters and over reported their use of the gel. This was clear from the drug levels not matching the self reported numbers. One of the differences in this study is that they only enrolled women due to the common perception that men and women do not work in conjunction to address these issues in this location. The mechanics of the sexual activity naturally result in one of the sexual partners being subject to greater harm. For instance, pregnancy is a confounder which may theoretically increase the acquisition of HIV/AIDS since the body is in an immunocompromised state. High risk sex indirectly leads to increased risk of acquisition of HIV/AIDS. The CAPRISA study did not explore whether the use of tenofovir in combination with other ARVs such as emtricitabine would offer more protection against HIV/AIDS.

Strengths

One strength of the CAPRISA trial is the blinding aspect of being able to use gels so it could look like everyone is taking the same substance (Karim et al., 2010). The authors were able to blind the participants to the use of the tenofovir versus the placebo gel. This eliminated some of the potential bias and risk compensation behaviors that were seen in the study by Grant et al. (2010).
Another strength of this study is the analysis models used that account for risk compensation.

**Safety**

In the CAPRISA trial, overall there was a very little increase in the rate of side effects with the use of tenofovir gel (Karim et al., 2010). More diarrhea and gastrointestinal infections were reported among the participants using the tenofovir gel, but otherwise adverse events and other safety markers were very similar between the two study arms. No safety concerns were identified in the 22 women exposed to tenofovir gel in early pregnancy. No congenital abnormalities were seen in the babies born during the study. TDF has been shown to cause decreases in renal function. Whether this serves as a confounder of renal impairment, this will remain unknown because women with renal impairment were excluded from the CAPRISA study. In both the tenofovir and in the placebo arm, no evidence of tenofovir resistance was found. Liver side effects or increases in hepatic flares were not seen during the study, possibly because of the low systemic absorption of the tenofovir gel epicutaneously. In conclusion, no substantial safety concerns were found with the use of vaginal tenofovir gel and it was well tolerated across the board.

In the iPrEx trial, side effects from FTC-TDF were mild and sparse (Grant et al., 2010). The most common side effect reported were nausea and unintentional weight loss of greater than five percent. Both were reported more frequently in the FTC-TDF group than the placebo group. No FTC or TDF resistance occurred in any of the participants who became infected with
HIV/AIDS during the trial. A mild increase in creatinine levels suggestive of renal impairment were observed in the FTC-TDF group but were self limiting and were not confirmed on specific repeat testing (Grant et al., 2010). Self reported HIV/AIDS sexual risk behavior decreased in both arms of the study. To conclude, daily use of PrEP of FTC-TDF appears safe and is well tolerated.

GRADE

Clinical guidelines are only as good as the evidence and judgments they are based upon. GRADE is a guideline and evaluation tool used to rate the quality of a body of evidence (Guyatt et al., 2008). GRADE helps guide clinicians in making informed cognizant healthcare management decisions that aim at causing no harm to the patient. GRADE was developed by a group of individuals worldwide. It clearly separates between quality of evidence and strength of recommendation (Guyatt et al., 2008). Determining the quality of evidence is crucial when making medical decisions on the behalf of one’s patients. GRADE does this by categorizing the quality of evidence from high to very low making it obvious for clinicians to understand the merit in the evidence. The recommendation is rated as either strong or weak to aid the clinician in making the best possible health management decision (Guyatt et al., 2008). The two studies analyzed were rated as high quality evidence originally and remained high because they had few study limitations, the results were consistent, the evidence was direct with precision, and they lacked reporting biases (Appendix: GRADE table). The recommendation for these studies was strong because the effects of the pharmacological interventions were desirable with low side effects.
Conclusion

The HIV/AIDS pandemic is indeed global, although its primary distribution is in sub-Saharan Africa (UNAIDS, 2010). Controlling the spread of HIV/AIDS has been a vexing and labyrinthine epidemiological health crisis that has not in three decades been conquered. According to Wohl (2010), keeping one person’s virus laden fluids away from the vulnerable cells of another is something most with a well developed frontal cortex can figure out how to do…yet we as a globe have yet to prevail a cure. The unchanged magnitude of new infections each year clearly demarcates the need for pioneering superior prevention strategies and care programs. Comprehensive and targeted HIV/AIDS prevention strategies is key to reversing this pandemic which includes exploring the test and treat approach (El-Sadr, 2010). Embarking on such an effort as eradicating HIV/AIDS will require a cascade of events beyond formulating a pharmacological agent. Exercising the use of the current ARV drugs used to treat HIV/AIDS may soon become the new chemical condom. Currently, it has yet to be completely proven to be the magic grenade to bringing the HIV/AIDS pandemic to adjournment, but the future is promising. Based on the findings in this systematic review, clinicians should consider recommending ARV PrEP combination therapy to high risk patients to prevent the acquisition of HIV/AIDS. In both studies, the cumulative probability of HIV/AIDS acquisition in patients who received ARV PrEP was substantially lower than the placebo group. This advance in HIV/AIDS prevention research may seem like a small preventative effect statistically, but it is rather significant considering we have had nothing that has shown a promising
decline besides abstinence and condom use. Much more work lies ahead thus the many studies in the pipeline, but at least a good starting point has been established.

Direction of future research might encompass anal sex transmission rates and HIV/AIDS when using a microbicide. The use of FTC-TDF or other ARVs in women and post exposure chemoprophylaxis therapy are also other avenues to be further explored.
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APPENDIX
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Table 1: GRADE Table