

# Discussion Paper

## *HIV Pre-Exposure Prophylaxis*

June 2004

### Summary

1. Pre-exposure chemoprophylaxis (PREP) – involves the provision of antiretroviral drugs to those at risk of HIV infection in order to prevent HIV infection occurring.
2. Current consensus is that an effective HIV vaccine is unlikely to become available in the next ten years. PREP has similar goals to a prevention vaccine. However to be effective it requires those at risk to take antiviral medications before every exposure to HIV. PREP is available now for some settings and has already been shown to be highly effective in preventing children from acquiring HIV at birth and from breast-feeding from HIV-positive mothers.
3. If PREP could be shown to be 100% effective, safe and cheap then its use as a prevention strategy would be universally supported. However it is more likely that PREP will:
  - be partially effective (i.e. less than 100% effective) Few, if any treatments or vaccines are 100% effective – for PREP agents the degree of effectiveness is a pivotal question;
  - have at least some associated toxicities (and often the long-term toxicity of PREP agents may not be known), some of which could be serious; and
  - be expensive (at least in the short term) – although this needs to be balanced against the significant costs of new HIV infections.
4. This means there are significant policy and implementation questions about how best to use PREP in different settings. A number of international trials for PREP are underway. These will provide some answers to questions about the effectiveness and short-term safety of PREP agents. They won't provide answers about the impact of the widespread introduction of a partially effective PREP agent in places where the rate of condom use is high, such as communities of gay men in Australia.
5. As research and clinical trials continue over the next few years there will be increasing information about the effectiveness of PREP. AFAO believes it is important that Australia moves promptly to develop an appropriate policy response to PREP and to identify further research questions that may need to be answered before PREP could be introduced.
6. When HIV prevention vaccines first began to be developed there was a national summit, a widespread debate and an Australian policy and research response. AFAO believes a similar debate and policy response is needed for PREP and recommends that the Commonwealth Health Department establish an expert working party and/or possibly convene a national meeting on PREP.



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## PURPOSE OF THIS DISCUSSION PAPER

This paper is an edited (with permission) version of a paper prepared by Stephen Gallagher for the ACON board.

This paper provides some background information on the candidate drug most likely to be used (tenofovir), and should not be taken to infer criticism of a valuable therapeutic agent. However, some information on what we now know about toxicities associated with ongoing use is critical in formulating a position on tenofovir as an HIV prophylactic.

## BACKGROUND

The possibility of a clinical study to investigate the viability, safety and efficacy of Pre-exposure prophylaxis (PREP) to prevent HIV infection among HIV negative individuals was raised at the Australasian Society of HIV Medicine Conference held in Cairns during October 2003. The candidate drug for any potential study at this stage is likely to be Viread © (or tenofovir *disoproxil fumarate*). Tenofovir is already under investigation as an HIV prophylaxis (preventative agent) among sex workers in Cambodia and Uganda (both funded by the Bill Gates Foundation). A clinical study into the safety and efficacy of tenofovir as an HIV prophylaxis among men who have sex with men was announced by the Center for Disease Control (CDC) in Atlanta on the 17<sup>th</sup> May this year<sup>1</sup> and is currently recruiting. Dr Mike Youle, principal researcher at the Royal Free Hospital in the UK publicly called for a trial of approved HIV anti-retrovirals for use as prevention agents for HIV negative (-ve) partners of HIV positive (+ve) people earlier this week. These studies overseas and calls for further studies by such esteemed researchers as Mike Youle point to the very real possibility that similar studies will soon occur in Australia.

Tenofovir (Viread ©) is licensed for use in combination with other drugs in Australia for people living with HIV/AIDS who are no longer receiving benefit from other approved HIV anti-retroviral drugs. Tenofovir belongs to the reverse transcriptase inhibitor group of drugs, however, it is unique and unlike other approved agents, tenofovir is a nucleotide rather than nucleoside analogue. Effectively it is a 'pro-drug'; chemically partially activated requiring less activation by the liver to 'break it down' and disseminate.

In theory this formula should present fewer toxicities and a better side effect profile, making it a better candidate for long term use both therapeutically and as a prophylaxis. Although well tolerated with side effects limited for the most part to diarrhoea, nausea and flatulence the long-term toxicities are not well understood as tenofovir has only been approved in the US since late 2001. There have been some reports of kidney toxicities associated with tenofovir – including kidney failure. It is not known if the incidence of kidney toxicity increases with time on the drug. Usefully both as a therapeutic agent and potential prophylaxis, tenofovir has a simple dosing requirement of one pill, once a day with or without food.

The data on tenofovir as a prophylactic agent thus far is limited but has shown to be effective against SIV (simian immunodeficiency virus) among macaque monkeys<sup>2</sup>. At ASHM, there was a report of a then unpublished trial showed the effectiveness of chemoprophylaxis in preventing transmission of HIV from breast-feeding mothers to their infants.

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<sup>1</sup> Randomised placebo-control, multi site study comprising of 100-200 HIV negative men who have engaged/engage in risk behaviours with HIV+ve man/men in preceding 3/6 months. Risk reduction counselling conducted prior to and during study to include condom use reaffirmation. Study participants will be followed from 18-24 months. Although eligibility criteria does not specify ethnicity African/American men are actively being recruited. Interestingly recruitment has fallen far short of 10% of total 200 participants thus far.

<sup>2</sup> HIV Guidelines, Perinatal HIV Transmission Prevention, New York State Department of Health AIDS Institute

## ISSUES ASSOCIATED WITH PREP

### Issue 1: The research strategy

**Double blind placebo based trials**<sup>3</sup> are being conducted or planned to measure the effectiveness and safety of a PREP agent. While double blind placebo trials are the most effective way to measure effectiveness and short-term safety – they do not measure the impact on behaviour when participants are unblinded. A key question about the decision to introduce a partially effective chemo prophylactic agent is what impact this is likely to have on the risk taking behaviours of those taking the drug.

Because tenofovir has those side effects common to most HIV antiretroviral drugs, any participant experiencing nausea, flatulence or diarrhoea may ascribe these conditions to the drug, when in fact they are experiencing a placebo effect<sup>4</sup>, or there may be some other reason for their symptoms. Thus participants may rightly or wrongly guess that are (or are not) on actual drug. If they guess they are on actual drug they may take more behavioural risks than they otherwise would both putting them at risk and potentially biasing the trial result. It will be necessary for the trial procedures to provide education and information about this.

Determining **participant eligibility criteria** for trials involving gay men is also difficult. Part of the purpose of the trialling process is to test PREP in those people for whom it is planned to make PREP available. Various suggestion have been made about who this might be including 'all sexually active HIV-negative gay men', 'negative men with HIV-positive partners', or 'HIV-negative gay men most at risk of HIV infection' (though how this is determined is not simple). The trials can only measure effectiveness if participants continue to place themselves at risk of HIV infection. Participation in the trial may influence risk-taking behaviour. This leads to both ethical questions and questions of appropriate trial design. These are similar to those questions faced in HIV prevention vaccine trial design – but in PREP participants are more likely to think that PREP will provide them with actual protection and are more likely to think they know they are on actual drug rather than placebo.

The criteria stipulated by the CDC in Atlanta for the US Study are:

- Healthy male; age>18 years old
- HIV sero-negative: give informed consent
- Engaged in unprotected receptive or insertive anal intercourse with HIV-positive or serostatus unknown male partner(s) within prior 3 to 6 months.

There are other questions about trial design. In the event that the trial is unsuccessful: will follow-up monitoring be available, especially in relation to kidney function? And of course in the event of the trial outcomes being successful but the drug not approved for subsidy by the PBS, how long will participants be eligible to receive the drug after the cessation of the trial? Until a successful PBS subsidised prophylactic formulation or vaccine is available? For a delimited period, or indefinitely?

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<sup>3</sup> A trial where the participant and the managing physician do not know whether the active agent or the placebo are being administered

<sup>4</sup> A physical or emotional change, which occurs after a substance is administered that is not necessarily a result of taking the substance. Such changes may be beneficial or harmful reflecting the expectations of the individual.

A further key point for trials is examining continuous dosing versus intermittent dosing (that is taking the drug before potential exposure). Of course there are numerous problems with intermittent dosing – risk activity is not always planned – but there are also considerable benefits in terms of cost, less potential side effects, target group acceptance and perhaps even increased compliance. Even if intermittent therapy is felt to be unwise, potential users of PREP who, say, have sex intermittently – for example only on weekends - are likely to work out that intermittent PREP is more appropriate for them and do it even if it is not recommended. Therefore intermittent therapy needs to be factored into trial design.

## **Issue 2: Potential impact on safe sex culture:**

### *a) Impact of trials on the broader safe sex culture*

A preventative study runs the real risk of being misunderstood by some gay men who while not participating may be aware of aspects of the study. How this will effect sexual decision-making is unclear. There has also been some speculation about the potential effect of PREP on the commitment of gay men to safe sex. Prior to the availability of PEP there was concern about its impact on safe sex practices. Also, some people have raised potential confusion about the differences between PREP and PEP. Clearly, this speculation in the absence of behavioural and attitudinal data points to its need. The lesson learned from PEP is that community awareness activities should commence well before any new technology such as PREP becomes available. Data collection on beliefs about PREP and clear education messages based on the findings of people's beliefs should be addressed before any study commences to allay the possibility of misunderstanding about sexual decision making in light of PREP and PEP.

PEP, however, is quite different from PREP. PEP education pointed out the hassle of taking triple combination for a month and that it came with no guarantee of preventing infection. PEP is rightly often perceived as onerous and unpleasant – but worth it if it prevent HIV infection. It is quite likely that PREP – involving one pill not associated with the side effects of triple combination – will be viewed much more favourably.

### *b) Impact of the widespread availability of PREP on the broader safe sex culture.*

There have been a number of modelling exercises on the potential impact of the introduction of a partially effective prevention technology – in particular in relation to say a partially effective microbicide. Not surprisingly, what these models predict is that in locations with low rates of condom use the widespread use of a partially effective HIV prevention technology is likely to reduce new HIV transmissions. However, in locations with high rates of condom use most of these models predict that where the widespread introduction of a HIV prevention technology resulted in significantly less condom use the impact – depending on what assumptions you make – may actually increase HIV transmissions. This is probably the major concern of community organisations and it is imperative that the trialling process attempts to monitor likely impacts as this will be a vital component of any decision to introduce partially effective PREP.

## **Issue 3: Long term toxicities of PREP agents**

### *a) tenofovir*

Tenofovir is currently the most likely candidate as a PREP agent – because of its long half life (i.e. effective levels stay in the body for longer periods) and because of its good safety profile. However, concerns about tenofovir's safety are starting to emerge.

Evidence of kidney dysfunction has been observed as a long-term toxicity of the closely related compound adefovir. Reports of tenofovir-associated renal toxicity among people living with HIV/AIDS have emerged. In one case report, a woman developed renal failure<sup>5</sup> after changing to tenofovir in a regimen that also contained Kaletra and didanosine (ddl). Whether this is a result of an interaction derived from this combination of drugs is unclear. Other case reports described people with stable chronic renal disease who developed renal failure<sup>6</sup> and died<sup>7</sup> after tenofovir was added to their regimens.

A larger, more recent retrospective study examined the records of 389 people living with HIV/AIDS in the tenofovir expanded access program. Five people discontinued tenofovir due to elevated creatinine levels. Follow-up of this cohort continues due to concerns about tenofovir's long term nephrotoxicity. In another study<sup>8</sup> 5% of people taking tenofovir experienced clinically relevant elevated creatinine<sup>9</sup> levels.

Various nucleoside analogue toxicities are thought also to apply to tenofovir in long-term use even though it's a nucleotide analogue. These toxicities are lactic acidosis<sup>10</sup>, mitochondrial abnormalities<sup>11</sup> and lipodystrophy.

#### *b) In general*

It is often the case that long-term toxicities of HIV antiviral drugs do not get adequately described until they have been in use for some time. Given that PREP agents could be used either continuously or intermittently over periods of years then comprehensive ongoing monitoring studies need to be an essential component of any clinical studies and wider implementation scheme.

### **Issue 4: Regulatory issues**

#### ***a) Licensing/Payment options/ PBS schedule***

Even in the event of tenofovir receiving marketing approval by the TGA as an HIV prophylaxis very comprehensive data would be required to demonstrate cost-effectiveness and to meet other criteria required for PBS listing. Gathering such data would be extremely difficult, as it has been in the case of PEP (which is not PBS listed). The Australian government is trying to rein in pharmaceutical drug costs; more and more stringent measures are being enforced in the prescription of PBS drugs. Highly specialised and expensive drugs such as tenofovir are subsidised for the most part because of their therapeutic effects. The likelihood of subsidising a 'lifestyle' choice drug is remote.

The current cost of tenofovir to the PBS is \$525 for thirty days supply. (i.e. 17.50 per tablet) At \$6,300 per annum realistically, the possibility of the emergence of a 'blackmarket' for tenofovir, in real terms is unlikely. These estimates change if tenofovir were able to be taken intermittently. The likelihood of people living with HIV/AIDS providing their prescribed,

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<sup>5</sup> Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: A first case report. *Am J Kidney Dis* 2002; 40:1331-3.

<sup>6</sup> Coca S, Perazella MA. Rapid communication: Acute renal failure associated with tenofovir: Evidence of drug-induced nephrotoxicity. *Am J Med Sci* 2002;324:342-4.

<sup>7</sup> Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis* 2003;36:1082-5.

<sup>8</sup> Harris M, Zalunardo N, Yip B, et al. Nephrotoxicity of tenofovir DF. *Can J Infect Dis* 2003; 14(suppl A): 25A.

<sup>9</sup> Creatinine is a substance formed from the metabolism of creatine which is found in blood, urine and muscle tissue as a result of metabolic processes used in 'breaking' down nitrogen essential to the production of protein. Elevated levels indicate kidney dysfunction/damage.

<sup>10</sup> A disorder characterised by increased accumulation of lactic acid in the blood, resulting in liver impairment, respiratory failure, neoplasms (tumours), and cardiovascular disease. All of which may be fatal without prompt medical attention.

<sup>11</sup> Mitochondria: essential organelles contained in cytoplasm (cell substance excluding nucleus)

subsidised therapeutic drug as prophylaxis to sexual partners or friends is unknown, but it is not likely to be high.

Post Exposure Prophylaxis (PEP) is not subsidised by the PBS and is reliant upon NSW Health covering the associated costs. This is derived from discretionary budgets at an Area Health Service (AHS) level. Some have argued that should an AHS decide to cover the cost of prophylactic tenofovir for people at risk of HIV infection (eg sero-negative partners of HIV +ve people), the AHS's AIDS budget would be in jeopardy, diverting attention from the real needs of people living with HIV/AIDS. Once again as an on-going option this is highly unlikely due to budget restraints.

The annual cost of \$6,300 does not include the associated costs of appropriate PREP pre screening, nor ongoing clinical monitoring. The hidden costs making it less likely for any level of government to cover PREP related costs. However intermittent therapy would dramatically reduce the drug cost and could partially reduce monitoring costs.

### **Issue 5: Implementation questions**

It is most likely that any PREP agent will not be 100% effective. However, it is also likely that PREP agents are more likely to offer a much higher level of protection than current HIV prevention vaccines under development. PREP agents could also become available long before vaccines. The questions about the best ways to use any PREP agent that is not 100% effective are complex and need to be the questions that are considered as part of the national debate AFAO is urging.

Unlike a vaccine, PREP relies on daily compliance of those at risk if on continuous therapy or effective intermittent therapy - so under non-trial conditions the actual effectiveness may be less than that obtained through clinical trials. Poor compliance and inconsistent dosing leads to sub-optimal serum levels, most likely too low to confer protection from HIV infection. The necessary serum concentration when used to treat people living with HIV/AIDS is reached within 25 minutes to an hour when taken on an empty stomach. It is possible that individuals may take their pills after any risk taking behaviour... that is effectively using PREP agents as PEP.

These issues point to the need for effective education about PREP as part of its implementation.

### **IS PREP ALREADY HAPPENING?**

Rumours about HIV-ve men taking HIV anti-retrovirals as HIV prophylaxis before a party weekend, or planned sexual event have been circulating for some time. Whether this practice is occurring is unknown. Answers to these questions were sought from 13 people who may be aware of such occurrences: most responded saying that they too had heard of similar claims from reasonably reliable sources, but nothing concrete has emerged.

While underground use of PREP may or may not be occurring and current usage is likely to be very low – it is likely that PREP will emerge as an issue in the future – particularly if trials show PREP provides a high level of protection, and PREP agents remain unsubsidised for this use.

## CONCLUDING REMARKS

Important data on the effectiveness or otherwise of PREP in preventing HIV infection in an individual is likely to become available over the next three years. It is unlikely that in that time frame that the true long term side effects of PREP will be known. It took decades for the side effects associated with the long-term use of contraceptives to be fully understood.

It is unlikely that any PREP agent will be 100% effective – but given available data from similar contexts it is possible that high levels of effectiveness can be achieved.

This means there are significant questions to be answered such as:

- Who could most benefit from PREP? Should it be offered selectively or widely within at risk populations?
- Who should pay for PREP, and indeed should governments pay at all?
- How can PREP be administered in order to minimise its impact on risk practices?
- Will men who are putting themselves at high risk of HIV infection be prepared to take a once daily pill in order to decrease this risk, or alternatively would they be able to manage intermittent therapy where therapy is timed according to their risk activities?
- What level of evidence would be needed on effectiveness, toxicities and likely community and behavioural impacts before any recommendation about widespread use of PREP could be considered? (in the absence of good data about long-term toxicity – there is a large difference between side effects of medicines that are treating illnesses and side effects of medicines in an individual that are to prevent potential illness)

Australia has no choice but to attempt to answer these questions while the trialling process is underway.