

Strategies for HIV Prevention and the potential for a vaginal gel

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Since the first public report of AIDS on the 5th of June in 1981 and the subsequent identification of the responsible retrovirus, the world has watched the unfolding pandemic.^{1,2,3} Major breakthroughs have been made in HIV treatment but a cure seems a long way off and the role of prevention is still paramount.³

Recently released study data suggests the drug Tenofovir, used as a vaginal gel, could have a role in preventing male to female HIV-1 transmission.⁴ Is this intervention the mythical silver bullet we have been waiting for or will it fail to have a practical application?

The Epidemic

It is estimated that around 60 million individuals have been infected with HIV worldwide with approximately 25 million deaths.^{2,3} Despite education programmes and barrier contraception, the numbers continue to rise.^{2,3} It is estimated that for every two people starting treatment, a further 5 become infected with the virus.^{2,3}

In sub Saharan Africa it is estimated 22.4 million people are infected with HIV.^{2,5} In 2008, there were 1.9 million new infections and 2.9 million people receiving anti-retroviral therapy (ART). However, a staggering 6.7 million might benefit from ART.^{2,3,5} Clearly, with the shortage of ART, prevention is still the key to disease control.

Considering regional modes of transmission is vital when considering prevention strategies. In Sub Saharan Africa, HIV is predominantly spread via sexual contact and mother to child transmission.^{2,3,5} However, in Eastern Europe and Central Asia, where there's been a 66% increase in those living with HIV from 2001 to 2008, there's a high prevalence among injecting drug users (Ukraine 38.5-50.3%, Russian Federation 37%).⁵ Prevention strategies focusing only on sexual transmission are inappropriate.

Strategies for the future

Few trials have shown success in preventing HIV transmission.^{3,4} However, 6 randomised control trials suggest further work is needed on.^{3,4}:

1. Male Circumcision
2. Vaccination
3. STI Treatment
4. Antiretroviral Microbicide

Each approach has shown statistically significant results, however, none have shown 100% protection.

As discussed above, the relevance of prevention strategies vary locally with the predominant modes of transmission. With sexual transmission, the rates of male to female transmission (1 in 200 to 1 in 2000) v. female to male transmission (1 in 700 to 1 in 3000) vary, therefore, a strategy targeting the former will have a greater impact potentially.⁶ Also, if women are protected in this way, it will reduce mother to child transmission.

Male Circumcision

When combined, three randomised control trials conducted in Africa (2002-2006) reported an overall 57% reduction in HIV acquisition (range 51% - 61%).⁷ Circumcision is believed to reduce HIV infection rates⁸:

1. Foreskin hosts abundant numbers of HIV target cells (Langerhans' and dendritic cells, CD4+ T cells and macrophages).⁸
2. The inner preputial mucosa consists of unkeratinised cells leaving it vulnerable to HIV infection.⁸
3. During intercourse, the foreskin is retracted over the shaft thus, exposing it to vaginal/cervical secretions, menstrual blood etc.⁸
4. Trauma in the form of microtears can occur during intercourse. The frenulum is particularly vulnerable and microtears provide a route of access for the virus.⁸
5. Uncircumcised men exhibit higher rates of genital ulcer disease, again, providing routes of entry.⁸

Success was shown only in reducing female to male infection with no significant results in the reduction of male to female transmission.^{7,8} One of the benefits in this strategy is that circumcision is a single, lifetime prevention measure.⁸ Following these results the WHO/UNAIDS recommended male circumcision be part of the HIV prevention package listing 13 countries in East and South Africa where this should be implemented as a priority⁸. Each country had high HIV prevalence, low circumcision rates and generalised heterosexual epidemics.⁸

The aim was to achieve 80% circumcision prevalence in target populations within a set time period. However, to date, in most cases this target hasn't been achieved.⁸

One important consideration when implementing this strategy is regulating who, where and how the circumcision is carried out.

Currently in Africa, circumcision is mostly carried out in the community by traditional medical practitioners. These practitioners are unlikely to be qualified to western standards and it's unlikely that procedures are carried out using sterile equipment. There is the risk therefore, that instead of protecting people, many, including babies and young children, may be put at risk of contracting HIV during the procedure itself. Also, anaesthesia may not be available. Should a procedure be recommended which may not be carried out humanely which also potentially puts individuals at risk of infection? Clearly, regulation of the procedure and training of practitioners is important as well as its success as an HIV infection preventative strategy.

Vaccine

With effective treatment, it is possible to suppress patient viral load to undetectable levels, reducing infectivity.⁹ Although risk is reduced, 100% protection isn't offered to a HIV negative partner.¹⁰ Common thinking is that a vaccine is the only way forward.^{1,9}

More than 25 years on from identification of the virus, a vaccine eludes us. Vaccine development is a firmly established science, but the nature of this virus causes a hurdle that science cannot yet overcome. Main difficulties:

1. No significantly large population identified who have developed resistance to HIV through natural immune response therefore, protective immune parameters not observed.^{10,11}

2. Identification of immunogens leading to broad, long lasting immunity yet to be established.^{10,11}
3. Antigenic drift – one of the main obstacles in vaccine development. Virus mutation rate is exceptionally high making it difficult to create one vaccine giving universal protection against all clades and strains.^{10,11}
4. Limitations of animal models. Although valuable information has been gained from animal models, there are differences in the viruses themselves (HIV vs. SIV) that could affect vaccine development. Although the gene Vpr is found in both viruses, its function differs greatly.^{10,11} Some HIV strains do cause disease in primates. However, they appear to be generally resistant to the CCR5-tropic primary isolates responsible for most human infection suggesting both the viruses themselves and the host immune response can differ. Therefore, for effective vaccine development, human trials are necessary.^{10,11}

The virus's natural ability to evade the host's immune response poses a problem in vaccine development.¹⁰ The viral envelope is most accessible to the host immune system but has evolved to go unnoticed.^{6,10} Key portions of proteins can be masked, including CD4 and co-receptor binding sites.^{6,10} The envelope itself is conformationally active, hiding antibody and B-cell recognition structures during virus-receptor binding.^{6,10} It has also been suggested that decoy mechanisms can be employed by the envelope to divert attention away from critical proteins required in virus – host binding. Displaying proteins likely to evoke an immune response on non-vital areas of the envelope, the virus protects binding sites from attack.^{10,11} Gp120 can undergo conformational change and be masked by a carbohydrate cloak allowing escape immune system detection.^{6,10,11}

There has yet to be a confirmed case of natural immune clearance of HIV. A vaccine would aim to prime the immune system in preparation for challenge by the virus. However, if the immune system has never been known to have the ability to neutralise HIV infection, is a vaccine possible?¹⁰

It's been suggested that the vaccine should stimulate multiple components of the immune response - the approach that current vaccine development has taken including the recent Thai vaccine trial.^{9,10,11}

The trial recruited 16,395 subjects (16-30 years old), deemed at community risk of infection, and was set up as randomized and double-blinded.⁹ Vaccinations were given over 24 weeks and subjects were followed up for 3 years.⁹

At 42 months, 14,672 subjects had completed the trial and were sero-negative.⁹

Of the subjects who completed the trial, 132 had contracted HIV (56 - vaccine group, 76 – placebo group).⁹ Of these, 7 subjects were later excluded as it was found they were infected between the HIV test and administration of the 1st vaccination.⁹ Using the Kaplan-Meier test, vaccine efficacy was 31.2% (95% CI, P= 0.04).⁹ This result was deemed to be significant however, only moderately.

Viral load in subjects who contracted HIV despite receiving the vaccine was virtually identical to those who received the placebo.⁹ This was considered worrying as it would be expected that viral load should be at least reduced.

Despite obvious difficulties in HIV vaccine development, the success of the Thai trial has delivered hope that a future vaccine may be possible.

STI Treatment

Several trials have taken place looking at STIs and HIV transmission risk. A Tanzanian study (1991-1994) reported success in reducing HIV infection in men who attended programme meetings to manage syndromic STI (adjusted IRR = 0.48, 95%CI 0.24-0.98, P=0.04).⁷ However, these results have never been replicated.⁷ One suggestion as to why this is the case includes the subsequent provision of superior HIV prevention advice in later trials giving better protection to future control groups.

Antiretroviral Microbicides

Trials of Microbicides have been undertaken since 1987 investigating their potential in HIV prevention. Until September 2010, no positive results were yielded. Microbicides are aimed at preventing HIV infection in women and are particularly important strategies in parts of the world where women are disempowered.⁴ Presently, 70% of HIV positive individuals reside in Sub Saharan Africa with women disproportionately affected (60%).⁴ 90% of new child infections also occur in this region, many from mother to child transmission.^{2,3,4} Protecting women against HIV protects both the individual and her future children.

Women's vulnerability to HIV in sub-Saharan Africa stems from their greater physiological susceptibility to heterosexual transmission and the severe social, legal and economic disadvantages present.^{4,5} A Lesotho study reported that the severe HIV epidemic experienced is likely to be due to the sexual and physical violence experienced by women in the country with 47% of men and 40% of women stating that women have no right to refuse sexual intercourse.⁵ Women are unable to negotiate condom use or monogamy giving them little control over their HIV status.^{4,5} The availability protection that women can use without the necessary compliance of their partner is paramount.

The Centre for the AIDS Program of Research in South Africa (CAPRISA) published results of the 004 trial in September 2010, which focussed the effectiveness and safety of a microbicide, Tenofovir gel⁴

The gel is inserted vaginally 12 hours before, and again, within 12 hours after intercourse.⁴ Efficacy was determined by compliance rates. In high adherers (>80%) HIV incidence was 54% lower than the control arm.⁴ In intermediate adherers (50-80%) and low adherers (< 50%), HIV incidence reduction was 38% and 28% respectively.⁴ Overall, there was 39% reduction in HIV incidence.⁴ The protective effect exhibited was irrespective of sexual behaviour, condom use, STI co-infection or urban/rural differences.⁴ Importantly, of those individuals who did seroconvert, there was no indication of Tenofovir resistance.⁴

Overall, this microbicide heralds an important step in HIV prevention. For the first time, a prevention strategy is available to a sector of the community which previously was at the mercy of its male counterparts, empowering women to protect themselves and their families.⁴ This strategy doesn't however offer a quick fix – it's an on-going strategy which must be used for every sexual encounter. Obviously, compliance issues are important in the efficacy of the strategy in the long term. As too is the on-going availability of the product to the individual. Each dose of the microbicide costs around 30 cents (USD) so per sex act, using 2 doses for 100% compliance, this will amount to 60 cents (USD).¹² Will governments in

developing countries be willing to absorb this cost and make available the product for general use? Many governmental positions in Africa are held by men – will a potentially expensive prevention strategy, only protecting women, be considered important enough to invest in? If women have to buy the product themselves, this will make it an unviable option for many.

Conclusion

It is clear there is still no one single method (beyond abstinence) offering 100% protection.

It is therefore appropriate that a prevention package be implemented which involves various strategies as a combined method of HIV prevention. When considering which strategies should be involved, along with efficacy, other considerations must be taken into account including cost, practical community application, local attitudes and product availability.

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