

## **HIV/AIDS Technologies:**

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A review of progress to date and current prospects

COMMISSIONED BY:

aids2031 Science and Technology Working Group

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# **aids2031 Science and Technology working group**

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## Acronyms

3TC	lamivudine
ANRS	Agence Nationale de Recherche sur la Sida
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	azidothymidine or zidovudine
bDNA	branched DNA
CDC	US Centers for Disease Control
CHER	Children with HIV Early Antiretroviral therapy (study)
CTL	Cytotoxic T-lymphocyte
D4T	stavudine
DSMB	Data and Safety Monitoring Board
EFV	Efavirenz
ELISA	Enzyme Linked Immunosorbent Assay
FDC	Fixed-dose combination
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HBAC	Home-based AIDS care
HCV	Hepatitis C virus
HPTN	HIV Prevention Trials Network
HSV-2	Herpes simplex virus type 2
IAVI	International AIDS Vaccine Initiative
IL-2	Interleukin-2
LED	Light-emitting diode
LPV/r	Lopinavir/ritonavir
MIRA	Methods for Improving Reproductive Health in Africa trial
MSF	Médecins sans Frontières
MSM	Men who have sex with men
MVA	Modified vaccinia Ankara
NIH	US National Institutes of Health
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OBT	Optimised background therapy
PCR	Polymerase chain reaction
PEPFAR	President's Emergency Plan for AIDS Relief
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
SIV	Simian immunodeficiency virus
SMART	Strategies for Management of Antiretroviral Therapy
TAG	Treatment Action Group
VOICE	Vaginal and Oral Interventions to Control the Epidemic trial

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## 2 Introduction

**aids2031** is a global initiative which seeks to explore actions which can be taken now in order to change the course of the epidemic before the year 2031, which will mark 50 years since the first case of AIDS was reported. Partners in the initiative are organized in nine working groups, each examining a different aspect of the epidemic. Working groups include: Modeling the Epidemic, Social Drivers, Programmatic Response, Leadership, Financing, Communication, Hyper-endemic Areas, Countries in Rapid Transition, and Science and Technology.

There is general consensus in the HIV/AIDS community that we must be more innovative and creative in our scientific approaches to successfully fight the epidemic. Results from several recent trials underscore the importance of working to understand the basic biology of the virus as well as the need to continue to develop innovative ways of combating it. In addition, challenges persist during the development of products, including ensuring community engagement in the design and management of biomedical prevention trials, designing interventions that are appropriate for developing world use, and encouraging continued commitments from industry to invest in non-traditional technologies. Finally, there is much that can be done during the development, roll out, and scale up of new technologies to ensure that all those in need have access to tools which may prevent, diagnose, or treat HIV/AIDS. The aids2031 Science and Technology Working Group is addressing these and other critical issues related to the discovery, development, and delivery of new HIV/AIDS technologies. Specifically, the working group will address three key questions:

1. What critical trends in discovery science and new technology may contribute to ending the pandemic or mitigating its human consequences?
2. What opportunities and challenges are associated with developing new science into products that prevent or treat HIV/AIDS?
3. How can we ensure that the introduction of new innovation results in timely access by those most critically affected by the AIDS pandemic?

The aids2031 Science and Technology Working Group is co-chaired by Dr. Christopher Elias (PATH) and Dr. Michael Merson (Duke Global Health Institute). Members of the working group include: Dr. Kevin De Cock (World Health Organization), Dr. Gordon Douglas (U.S. National Institutes of Health), Dr. José Esparza (Bill & Melinda Gates Foundation), Dr. Michael Free (PATH), Dr. NK Ganguly (Indian Council of Medical Research), Dr. Catherine Hankins (UNAIDS), Dr. Barton Haynes (Duke University), Dr. Sharon Hillier (University of Pittsburgh), Ms. Ellen t'Hoen (Médecins Sans Frontières), Professor Soulyemane Mboup (Université Cheikh Anta Diop), Dr. Joep Lange (University of Amsterdam), Dr. Veronica Miller (George Washington University), Dr. Lynn Morris (National Institute for Communicable Diseases, South Africa), Ms. Beatrice Were (Global AIDS Alliance), and Dr. Morenike Ukpong (Nigerian HIV Vaccine and Microbicides Advocacy Group).

This paper was commissioned as an introductory landscape analysis for the aids2031 Science and Technology Working Group, building on other recent landscape analysis work in the fields of HIV prevention technologies, therapeutics, and diagnostics. It is intended to provide a baseline for further discussion and to serve as a resource for the current status of



research and development for biomedical and other technological interventions to prevent, treat, and diagnose HIV/AIDS.

The paper was written by Keith Alcorn (Senior Editor, NAM), with particular thanks to Dr. Christopher Elias (PATH), Dr. Michael Merson (Duke University), Mitchell Warren (AIDS Vaccine Advocacy Coalition, or AVAC), Yvette Gerrans (PATH), Kaitlin Christenson (PATH), Thor Wagner (University of Washington), Polly Harrison (Alliance for Microbicide Development), and Christina Kramer (PATH) for their comments and insights. AVAC kindly permitted the reproduction of several tables illustrating timelines for results in HIV prevention trials from its website.

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### 3 Prevention technologies

This section builds on extensive work by the AIDS Vaccine Advocacy Coalition (AVAC) in monitoring the landscape of HIV prevention research, together with the report published from a September 2006 meeting convened by the Forum for Collaborative HIV Research, *A New Era for HIV Prevention?*<sup>1</sup>

That meeting reviewed prevention technologies undergoing trials and concluded that there was a need for better coordination between the various prevention research approaches in order to develop a prevention trials infrastructure, and to investigate multi-component interventions. The meeting also heard strong arguments about the need for prioritisation within the prevention technology field due to the large size of trials needed to prove efficacy, and due to the multiplicity of agents and potential combinations of interventions that might be available for study.

The meeting also anticipated a cluster of potential study results in 2007 and 2008 that might move the prevention technology field forward.

But since that meeting took place there have been a number of substantial setbacks in the field of HIV prevention technologies which have tempered previous optimism about the pipeline of HIV prevention technologies and their applicability in the field.

Specifically, the following trials have produced no evidence of effect, or a trend towards harm:

- CONRAD phase III study of cellulose sulphate (UsherCell) microbicide halted after interim analysis showed higher rate of HIV infection in UsherCell group (Family Health International study of UsherCell also halted due to CONRAD results).
- The Family Health International phase III study of the SAVVY microbicide in Nigeria was halted after interim analysis showed that SAVVY did not reduce the incidence of HIV infection when compared to placebo.
- MIRA female diaphragm and lubricant study completed, but no evidence of protective effect.
- HPTN 039 study of acyclovir suppressive therapy for HSV-2 and London School of Hygiene and Tropical Medicine trial of acyclovir suppressive therapy in women in Tanzania completed, but no evidence of protective effect.
- Population Council phase III study of Carraguard microbicide completed, but no evidence of protective effect.
- Higher concentration PRO 2000 arm abandoned in Microbicides Development Program phase III study due to futility.
- STEP proof-of-concept study of Merck Ad5 vaccine halted after interim analysis showed lack of protective effect.

Inevitably there will be setbacks in product development, especially where the correlates

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<sup>1</sup> Chris Collins, Meagan Lloyd, Veronica Miller. A new era for HIV prevention? Forum for Collaborative HIV Research, Washington DC, February 2007.

of protection are not well-established. Although these studies have not provided a prevention technology for further development, they have demonstrated the ability of multiple sponsors to run large trials of prevention technologies, and generated important information that will contribute to the design of future studies.

The only positive results in the past two years from HIV prevention efficacy trials have come from adult male circumcision studies in HIV-negative men.

### 3.1.1 ‘Combination prevention’

In a recently published supplement to *The Lancet*<sup>2</sup>, HIV prevention experts highlighted the range of interventions that will need to be considered as part of a comprehensive prevention response:

- Behavioural interventions.
- Biomedical interventions such as circumcision, vaccines and the use of antiretroviral drugs to prevent HIV infection.
- Structural interventions which act on the factors that make people more vulnerable to HIV infection, such as poverty, gender, stigma and discrimination.
- Optimisation of surveillance, planning, delivery, monitoring and evaluation.
- Leadership, governance, advocacy and resource mobilisation.

The supplement concludes with a call to action which emphasises the need for societies to fully implement ‘combination HIV prevention’.

For this vision to be fully realised, effective biomedical interventions in addition to condoms and circumcision need to be developed and implemented across a wide range of settings in addition to behavioural and structural interventions.

Furthermore, as Padian et al note, biomedical interventions need to be integrated with the other modes of prevention listed above. “These combination prevention strategies are needed to maintain adherence [and] to avoid sexual disinhibition (risk compensation),” they write<sup>3</sup>.

### 3.1.2 A new lexicon for biomedical HIV prevention?

Padian et al also argue that the taxonomy used to categorise biomedical prevention interventions is in need of revision. Categorising the use of antiretroviral drugs in HIV prevention according to the mode of administration – microbicide, pre-exposure prophylaxis, post-exposure prophylaxis, infant prophylaxis or treatment of HIV-positive individuals – undermines a more integrated approach to prevention of HIV transmission, they argue.

*“As with hormonal contraception as a method to prevent pregnancy, future assessments of prevention with antiretroviral drugs should focus on methods of delivery (oral, topical [vaginal, rectal], injectable), dosing regimen (daily, monthly, intermittent or exposure-related (before and afterwards), single versus combination products, and what works in specific target populations (defined by risk, behaviour*

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<sup>2</sup> HIV Prevention. *The Lancet*, August 2008.

<sup>3</sup> Padian NS et al. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *The Lancet* 372 (9638): 585-599, 2008.

*and infection status). The present terminology....is outdated and inefficient. It has resulted in separate scientific meetings, publications and discourse, and thus prevents a more integrated approach to prevention of HIV transmission.”<sup>4</sup>*

This paper groups antiretroviral prevention modalities together, but discusses each as a separate category due to their historical development.

### **3.1.3 Future questions for biomedical prevention trials**

A number of cross-cutting issues affect all biomedical prevention trials:

- The prevention and treatment standards of care are evolving – what effect will this have on future studies? How will circumcision affect the power and design of existing studies and those now planned? If any other biomedical prevention intervention is shown to have efficacy, how will this affect the design of microbicide, vaccine and other prevention studies?
- Are the standards of care yet sufficiently agreed globally for those screening or taking part in prevention trials? When implementation takes place, the prevention standard of care may not be available in all settings. How do trial designs address this contradiction?
- How will long-term access to successful products for trial participants be managed?
- Adherence and effectiveness are inextricably linked. How can adherence be improved? Adherence, the modifiable element in the use of any prevention technology, needs to be measured more carefully, and further research is needed on how to improve adherence, especially for those interventions that require high levels of adherence.
- Regulatory puzzles – how will regulators treat combination trials and how will this affect the speed of research? Will it be necessary to carry out phase II studies of combinations, or adequate to combine them at phase III level?
- Long-term safety – which assays will be appropriate for which products, and how lengthy should the follow-up be to determine the durability of efficacy? How will large studies of different product types need to be powered in order to detect long-term toxicities?
- Who will decide which studies have priority for funding if phase III studies eventually need to recruit 20,000 individuals and run for over five years? Should different approaches be better coordinated, e.g. is there a need for an HIV Prevention Research forum that is independent of donors? How might such a forum be reconciled with the ultimate responsibility that funding organizations have to the source of their funds? To what extent are donors shaping the HIV prevention research agenda? How will industry be engaged with priority-setting mechanisms?
- Who will coordinate operational research to accelerate wide delivery of successful prevention technologies?
- How can prevention technologies be studied in the context of comprehensive

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<sup>4</sup> Padian, *ibid.*

prevention responses that embrace not only the trial site, but the wider community? HIV treatment programmes have shown the importance of engaging with the community – would the power of biomedical interventions be enhanced if phase III studies looked at combinations not only of products, but of products and other community-led interventions, such as community-based adherence support?

- How can social science contribute to the development of effective biomedical interventions? How can greater insight be gained into the interaction of human beings with prevention technologies? For example, what can we learn from the changes in sexual behaviour among gay men since the introduction of HAART - this is not a mechanistic process of spontaneous disinhibition, but a complex network of messages and judgements between individuals as a consequence of the adoption of viral load testing, provision of 'undetectable' results to individuals and subsequent decision-making based on that information<sup>5</sup>.

### **3.1.4 Challenges in biomedical HIV prevention trials**

A comprehensive review of the methodological challenges in biomedical HIV prevention trials was recently carried out by an Institute of Medicine panel<sup>6</sup>. It identified a number of cross-cutting issues relevant to all biomedical prevention studies.

Lessons learned from prevention technology trials:

- Lower than estimated HIV incidence has been a feature of many studies; this will affect the size of study that needs to be run in the future, so accurate estimation of the baseline levels at trial sites will be essential. It should be based on direct longitudinal follow-up of individuals in the planned trial sites, and corroborated by at least one other source.
- Future studies will also need to be stratified by male circumcision status, further increasing the size and cost of such studies. If further prevention technologies prove to be effective, these will also need to be considered in the trial design.
- Adherence is often poor and measurement of adherence will be critical to determining the degree of potential benefit attached to an intervention that requires the volunteer to administer the intervention.
- High rates of loss to follow-up have been reported in some studies – lessons need to be learned about measures to reduce loss-to-follow-up in antiretroviral treatment programmes. There is also often poor adherence to study visit schedules.
- High pregnancy rates may lead to interruption of product use or administration, but the implications of this may vary according to product type. A protocol requirement to discontinue product use or administration if pregnant does not reflect the real world in which the product will be used. For some types of interventions, investigators should undertake pre-trial assessments of a product's potential effects on pregnant women and their fetuses to determine circumstances in which women that become pregnant during a trial might continue to use the study product.
- Communications, consultation and true partnership with affected communities are

<sup>5</sup> Rosengarten M et al. The challenges of technological innovation in HIV. *The Lancet* 372: 357-358, 2008.

<sup>6</sup> Stephen Lagakos, Alicia Grable (editors). *Methodological challenges in biomedical HIV prevention trials*. Institute of Medicine, February 2008.

essential in designing and preparing for trials, communicating changes in the trial protocol and explaining the results.

- Research infrastructure is vulnerable to domestic upheaval, which can occur even in countries that appear stable. Local political commitment can also affect trials. But prevention trial sites are precious resources, and the infrastructure investment now occurring with PEPFAR funding should not be wasted.
- Registration-level compliance at trial sites can be hard to achieve and requires extensive training, as does high quality laboratory support.

### **Institute of Medicine recommendations regarding biomedical HIV prevention trials (2008)<sup>7</sup>**

*From executive summary:*

- Key recommendations for conducting late-stage HIV prevention trials include monitoring the evolving results of a trial to ensure that it is maintaining the best interests of participants, adjusting the trial to improve adherence or other aspects of the study protocol, and using safety information that may become available from external sources.
- Design recommendations include: using endpoint-driven trials, considering inclusion of both blinded and unblinded control arms in future trials, collecting information for evaluating the effects of biomedical interventions on women who become pregnant during a trial and their fetuses, and selecting methods for evaluating product adherence and risk-taking behaviour.
- Recommendations for analyzing trial results include using participant adherence in evaluating the relationship between interventions and HIV risk, the practice of excluding results from participants judged to have been already infected at the time of enrolment, and accounting for product discontinuation due to pregnancy in the analysis of the risk of HIV infection.

Finally, in order to enable more efficient evaluations of biomedical interventions, the committee recommends that researchers give priority to developing biomarkers of recent HIV infection which can be used in cross-sectional samples to estimate HIV incidence rates, identifying surrogate markers for HIV infection and product activity that investigators can reliably use as intermediate trial endpoints, and exploring alternative trial designs that might answer important research questions more efficiently than the traditional two-arm superiority design.

#### **3.1.5 Behavioural prevention**

Although the agenda for behavioural prevention research is beyond the scope of this paper and outside the remit of the Science and Technology working group, developments in behavioural prevention will inevitably have an impact on the design and interpretation of biomedical HIV prevention studies.

In a recent review of the evidence on behavioural HIV prevention the Global HIV Prevention Working Group highlighted the elements common to successful HIV prevention programmes:

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<sup>7</sup> Lagakos, *ibid*.

*According to the available evidence ... effective strategies pursue a combination of behavior change approaches that are delivered with sufficient coverage, intensity, and duration, and that are tailored to address the main drivers of HIV transmission in national epidemics. Effective HIV prevention addresses the specific needs and circumstances of the target population and aims to affect multiple determinants of human behavior, including individual knowledge and motivations, interpersonal relationships, and societal norms. Community engagement and strong political support have been key ingredients of successful national efforts to change behavior to prevent HIV infection.*<sup>8</sup>

Despite this, the Global HIV Prevention Working Group notes that studies of behavioural interventions have tended to evaluate the behavioural and epidemiological impact of discrete interventions rather than looking at combinations of interventions.

They also note that future behavioural change programmes will continue to be dependent on technologies such as condoms, while the introduction of new technologies will require behavioural changes.

Innovative thinking about how to design studies of biomedical interventions that take into account the evolving standard of care in HIV prevention will be a key challenge for the development of new technologies. Designing studies that can produce robust, generalisable results while respecting local contexts in the study design will also be a challenge.

### **3.2 Male condoms**

Male condoms have long been recommended as protection against sexually transmitted infections, and even before HIV was isolated, gay men in North America and Europe had begun to use condoms during anal intercourse on the assumption that AIDS had a sexually transmitted aetiology.

The male condom remains one of the central technologies of HIV prevention today. A US National Institutes of Allergy and Infectious Disease review in 2001 concluded that male latex condoms are a highly effective barrier to transmission of particles similar in size to viruses, and have a low rate of breakage or slippage<sup>9</sup>. A systematic review by the Cochrane Collaboration analysed HIV seroconversion rates in longitudinal and cross-sectional studies of serodiscordant couples, comparing 'always' and 'never' users. The review concluded that consistent condom use had an efficacy of approximately 85%<sup>10</sup> in heterosexual couples.

The latex condom continues to dominate the global market, but polyurethane condoms

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8 Global HIV Prevention Working Group. Behavior change and HIV prevention: [Re]considerations for the 21st century. August 2008.

9 National Institute of Allergy and Infectious Diseases. Workshop summary: scientific evidence on condom effectiveness for sexually transmitted disease prevention. July 2001.

10 Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev 2002;(1):CD003255.

that may have greater sensitivity, better storage characteristics and compatibility with oil-based lubricants were introduced in the 1990s. Polyurethane condoms remain more expensive than latex condoms. A Cochrane systematic review noted a significantly higher breakage rate for non-latex synthetic condoms across ten randomised studies, and also observed that these condoms were significantly less likely to be recommended by users than their latex counterparts<sup>11</sup>.

UNFPA estimated in 2008 that donors had provided around 2 billion condoms<sup>12</sup> for HIV prevention and contraceptive purposes to sexually active men in sub-Saharan Africa in 2007, an increase of almost 50% since 2004, when UNFPA estimated that donor support was funding only 8 condoms per adult male aged 15-49 per year in the region<sup>13</sup>.

Implicit in many discussions of HIV prevention technologies is the assumption that female-initiated prevention methods require investment because men cannot, or will not, use condoms.

However, there has been little call for better condoms that will be used more widely by men.

The biggest disadvantage of the male condom is that its use requires male action to put on the condom and male satisfaction with the product to maintain consistent use. Quite apart from psychosocial barriers to condom use (such as the belief that condom use implies a lack of trust), a number of reasons for failure to use condoms relate to the technology itself:

- Loss of sensation and/or lubrication.
- Loss of erectile function. Loss of erection while putting on a condom and during intercourse has been correlated in several studies with unprotected sex<sup>14 15</sup>.
- Interruption of intimacy. Problems with packaging, and applying the condom, are frequently cited as an interruption of intimacy in anecdotal reports, an observation confirmed by Kinsey Institute research<sup>16</sup>.
- Condom size and fit: poor fitting condoms - and discomfort caused by poorly fitting condoms - are significantly correlated with condom failure and subsequent lower levels of use. This may be a particular issue for younger adolescents. Information on the distribution of penis sizes within various populations is more comprehensive for US populations than others<sup>17 18 19</sup>.

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11 Gallo MF, Grimes DA, Schulz KF. Non-latex versus latex male condoms for contraception (Cochrane Review) In: The Cochrane Library, Issue 2, 2003. Oxford.

12 UNFPA. Donor support for contraceptives and condoms for STI/HIV prevention 2007.

13 UNFPA. Donor support for contraceptives and condoms for STI/HIV prevention 2004.

14 Erection loss in association with condom use among young men attending a public STI clinic: potential correlates and implications for risk behaviour. *Sexual Health*, 2006; 3(4).

15 Lammers M et al. Condom induced erectile dysfunction (COINED): a unique predictor of deliberate sexual risk. XVII International AIDS Conference, THPDC205, Mexico City, 2008.

16 Crosby R et al. Condom-use errors and problems A neglected aspect of studies assessing condom effectiveness. *American Journal of Preventive Medicine* 24 (3): 367-370, 2003.

17 Spruyt, Alan B. User behaviors and characteristics related to condom failure. in *The Latex Condom: Recent Advances, Future*



- User error in applying condoms<sup>20</sup>. Thirty per cent of US male college students questioned put a condom on the wrong way round. Is this lack of education or a more fundamental design/packaging fault?<sup>21</sup>
- Unreliable, poor quality: quality assurance varies according to the source of the condoms. While donor-funded condoms are subject to strict procurement and storage requirements<sup>22</sup>, condoms bought over the counter, manufactured by local producers, may not be quality-assured in some countries.
- Lack of availability: despite comprehensive efforts to improve condom provision through social marketing<sup>23</sup>, respondents continue to cite lack of availability as a reason for not using condoms<sup>24</sup>.

Condom manufacturers and regulators have been seeking to address these issues through a number of approaches:

- Improving sensitivity, performance eg through use of polyurethane to increase sensitivity (e.g Durex Avanti, Trojan Supra), use of compounds to delay ejaculation (e.g. Durex Performa), prolong erection (Futura Medical/Durex CSD500, likely to be approved in Europe in 2008).
- Improving condom design to create a roomier condom head, to allow greater stimulation of nerve endings (Inspiral condom).
- Spray on condom<sup>25</sup> and other condom applicators designed to ease condom application; the Pronto condom, for example, is packaged in such a way as to allow easy packet opening and application to the penis in a single action<sup>26</sup>.
- Condom size and fit: 'They Fit' sized-to-fit condoms are available in 55 different sizes by mail order in the United States.
- Social marketing: The numerous organisations engaged in social marketing continue to accumulate valuable experience.

Despite these initiatives there is clearly a need for more research, in a variety of settings, into product characteristics that encourage or impede condom use, in order to inform innovations in condom use that will increase acceptability of condoms to men.

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Directions. Family Health International., 1998

18 Crosby R et al. Condom discomfort and associated problems with their use Among university students. *Journal of American College Health* 54(3) 143- 147, 2005.

19 Crosby R et al. Men With broken condoms: who and why? *Sexually Transmitted Infections*, 83 (1) 71-75, 2007.

20 Crosby R (2003), op cit.

21 Crosby R et al. Condom use errors and problems among college men. *Sexually Transmitted Diseases* 29 (9), 552-557, 2002.

22 WHO/UNAIDS/UNFPA/FHI. The male latex condom : specification and guidelines for condom procurement : 2003.

23 UNAIDS. Condom social marketing: selected case studies. 2000

24 Population Services International. Reasons for non-use of condoms in eight countries in sub-Saharan Africa. PSI Working Paper 49, 2002.

25 See [www.sprayonkondom.de](http://www.sprayonkondom.de)

26 See <http://www.prontocondoms.co.za/>

In 1998 Family Health International reviewed future research questions in the male condom field<sup>27</sup>. All the issues raised remain priorities for research ten years later. They include:

- More research to identify strong yet sensitive condoms acceptable to users.
- Refinement of testing protocols to improve quality assurance.
- More human behavioural research to disentangle the extent to which condom 'refusal' is driven by product characteristics.
- Better understanding of how communication and marketing strategies can promote consistent and successful condom use.
- How do men become satisfied and experienced condom users, and what can be learnt from them to improve education and product characteristics?
- What factors contribute to condom failure?

### **3.3 Harm reduction for injecting drug users**

Like condom use, elements of harm reduction for injecting drug users were initially pioneered through community-level intervention from 1984 onwards.

More formalised programmes of harm reductions began to emerge in Europe and North America in the late 1980s, and the World Health Organization now recommends that a comprehensive programme of harm reduction for injecting drug users should consist of the following elements<sup>28 29 30</sup>:

- Outreach to injecting drug users and their sexual partners and provision of information and education about HIV, harm reduction and coinfections.
- Syringe and needle exchange.
- Opioid substitution therapy.
- Voluntary counselling and testing, condom programming for IDUs and their sexual partners, and sexually transmitted infection treatment.
- Antiretroviral treatment.
- Diagnosis and management of coinfections including hepatitis and tuberculosis.

Despite the evidence supporting these interventions, political and public health resistance to elements of the recommended harm reduction package remains strong in some regions of the world experiencing serious HIV epidemics among injecting drug users<sup>31</sup>.

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27 McNeil E et al. Recommended research priorities, in: The latex condom: recent advances, future directions. Family Health International 1998.

28 World Health Organization. Policy and programming guide for HIV/AIDS prevention and care among injecting drug users. 2005.

29 World Health Organization. Evidence for action technical paper. Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users. 2004

30 World Health Organization. Evidence for action technical paper. Effectiveness of drug dependence treatment in prevention of HIV infection among injecting drug users. 2006.

31 Open Society Institute. Barriers to access: medication-assisted treatment and injection-driven HIV epidemics. April 2008.

### 3.3.1 Future research questions

The contribution of various elements of the recommended harm reduction package to reducing HIV incidence is still unclear, and a review conducted by the Institute of Medicine in 2005 concluded that there was a need for a multinational, multicentre study to address this question and to contribute to the international policy-making debate<sup>32</sup>.

The Institute of Medicine also concluded that cost-effectiveness analysis of opioid substitution therapy as an HIV prevention tool should be conducted in resource-limited countries with growing HIV epidemics among injecting drug users. Research into the best ways of convincing stakeholders to adopt proven harm reduction methods is also vital, the report noted.

There is remarkably little current research into technological interventions that might assist HIV harm reduction in injecting drug users.

**Opioid substitution therapy:** The NAOMI study (North American Opiate Medication Initiative) is enrolling participants at two sites—Vancouver and Montreal. About half of these volunteers will be assigned to receive pharmaceutical-grade heroin and half will receive methadone. Those in the heroin group will be treated for 12 months then transitioned, over three months into methadone maintenance, abstinence or other treatment programs of their choice. The study expects to report results in late 2008.

### 3.4 Circumcision

Observational research has long shown a relationship between lower prevalence of circumcision and higher prevalence of HIV, finding a population-level association between HIV infection and a lack of male circumcision in sub-Saharan Africa<sup>33</sup>, and a systematic review of 27 studies found that circumcised men had a 42% lower risk of HIV infection<sup>34</sup>.

Strong evidence exists from three randomised controlled trials undertaken in Kisumu, Kenya<sup>35</sup>, Rakai District, Uganda (funded by the US National Institutes of Health)<sup>36</sup>, and Orange Farm, South Africa (funded by the French National Agency for Research on AIDS)<sup>37</sup> that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60% after about 24 months of follow-up. The Kisumu trial has

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32 Committee on the Prevention of HIV Infection among Injecting Drug Users in High-Risk Countries. Preventing HIV infection among injecting drug users in high risk countries: an assessment of the evidence. National Academies Press, 2006.

33 Auvert B, Buvé A, Lagarde E, et al. Male circumcision and HIV infection in four cities in sub-Saharan Africa. 2001 Aug;15 Suppl 4:S31-40.

34 Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and metaanalysis. AIDS. 2000 Oct 20;14(15):2361-70

35 Bailey R et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial, Lancet 369: 643-56, 2007.

36 Gray RH et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial, The Lancet 369(9562):657-66, 2007.

37 Auvert B et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial, PLoS Med 2(11):e298, 2005.

recently reported that a reduction in risk of 64% persisted at 42 months of follow-up<sup>38</sup>.

Each intervention trial randomised adult, HIV-negative heterosexual male volunteers either to be circumcised by a medical professional at a clinic, or to no immediate intervention (no circumcision). All participants were extensively counselled in HIV prevention and risk reduction techniques.

Male circumcision for HIV prevention purposes is not recommended for HIV-positive men. An analysis from a separate Rakai study that investigated the possible protective effect for HIV-negative women from HIV-positive men undergoing circumcision indicated that there might be a heightened risk of HIV transmission to female partners of recently circumcised HIV-positive men if sexual activity took place shortly after surgery, presumably before the surgical wound is completely healed, highlighting a potential operational precaution in implementing circumcision as a prevention method<sup>39</sup>.

In March 2007 WHO and UNAIDS recommended that male circumcision should be incorporated into HIV prevention programmes in sub-Saharan Africa<sup>40</sup>, and PEPFAR is expected to provide around \$30 million in funding for circumcision interventions in eleven focus countries in 2008<sup>41</sup>.

### **3.4.1 Projected effect on the HIV epidemic**

Multiple models of the impact of male circumcision on HIV epidemics in sub-Saharan Africa have been produced and all show a substantial impact on HIV incidence and prevalence. An analysis using data from UNAIDS and the South African study estimated that if circumcision is taken up widely and the full effect seen in the South African study were to be replicated, 5.7 million HIV infections could be averted in sub-Saharan Africa over a 20-year time period<sup>42</sup>.

Another mathematical model shows that universal male circumcision would have the greatest impact on HIV incidence, but that targeting circumcision at men with the most sexual partners, and those aged between 20 – 30-years would be the most efficient way of reducing HIV prevalence. Modelling the effects of circumcision on HIV prevalence and incidence in sub-Saharan Africa between 2007 and 2020, Londish et al. projected that complete male circumcision in an average hyper-endemic country could reduce HIV prevalence in 2020 from 8.3% to 5.3% and incidence from 13.5 seroconversions per thousand to 7.3 per thousand<sup>43</sup>. Targeting only 20-to-30 year old men or men with greater sexual activity produced the most cost-effective reduction in HIV prevalence, 2.0% and

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38 Bailey RC, Moses S, Parker CB et al. The protective effect of male circumcision is sustained for at least 42 months: Results from the Kisumu, Kenya trial. XVII International AIDS Conference, 3-8 August 2008: Abstract THAC05.

39 Wawer M et al. Trial of circumcision in HIV+ men in Rakai, Uganda: effects in HIV+ men and women partners. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston. Abstract 33LB. 2008.

40 WHO/UNAIDS. New data on male circumcision and HIV prevention: policy and programme implications. WHO and UNAIDS technical consultation on male circumcision and HIV prevention: conclusions and recommendations. March 2007.

[http://www.who.int/hiv/pub/malecircumcision/research\\_implications/en/index.html](http://www.who.int/hiv/pub/malecircumcision/research_implications/en/index.html)

41 US President's Emergency Plan for AIDS Relief Accountability Report: Partnerships for Prevention.

[http://www.pepfar.gov/press/fourth\\_annual\\_report/99832.htm](http://www.pepfar.gov/press/fourth_annual_report/99832.htm)

42 Williams BG et al. The potential impact of male circumcision on HIV in Sub-Saharan Africa. PLoS Med 2006;3:3262.

43 Londish B et al. Mathematical modelling of male circumcision in sub-Saharan Africa predicts significant reduction in adult HIV prevalence even when it is limited to certain age groups. Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, abstract WEAC104, 2007.

1.1% respectively.

Finally, a review of published and unpublished modelling by an expert group convened by UNAIDS and WHO concluded that one HIV infection would be averted for every 5 to 15 male circumcisions carried out, using a 10-year horizon. If 90% of adult men are circumcised after ten years, HIV incidence in the population as a whole is projected to decline by 50% by the end of the period, and by 40% if 70% coverage is achieved<sup>44</sup>.

### 3.4.2 Circumcision technologies

Mass medical circumcision in sub-Saharan Africa will require the safe, hygienic delivery of circumcision in a wide range of settings and, because of human resource constraints, by personnel with widely varying medical training. Surgery is currently required for circumcision but the development of a non-surgical approach to safe male circumcision would dramatically alter the ability to deliver large numbers of circumcision safely.

A recent meeting convened by the Forum for Collaborative HIV Research, the Bill & Melinda Gates Foundation, UNAIDS, and WHO reviewed the landscape of current circumcision technologies, future developments and estimates of demand<sup>45</sup>.

The current methods most commonly employed in adult medical circumcision are:

- Forceps-guided method
- Dorsal slit
- Sleeve resection

All these methods require a degree of surgical skill, suturing and anaesthesia.

Neonatal circumcision is considerably easier. A number of clamping devices are available for use in infants and young boys, but no adult versions suitable for use in the field currently exist:

- Mogen clamp: device designed specifically for circumcision, this method removes less foreskin<sup>46</sup> and the device has the potential to trap part of the glans penis, leading to medical accident. Also requires suturing.
- Gomco clamp: bell-shaped device inserted beneath the foreskin, removes more foreskin than other methods, may minimise bleeding, but requires suturing.
- Necrosing clamp: single-use pre-sterilised plastic device or ligature that slides under the foreskin, which is then clamped, and the foreskin is either cut when numb or allowed to die due to deprivation of blood supply. Some manufacturers claim no bleeding occurs, hence less post-operative complications and no need for suturing. The device remains in place for up to ten days – this may be uncomfortable and there is potential for complication if erection or swelling occurs. With some devices there is

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44 Lohse N et al. Challenges in developing models to estimate the impact of male circumcision on the HIV epidemic. XVII International AIDS Conference, Mexico City, 2008.

45 Meeting the demand for male circumcision: an assessment of what is needed. Forum for Collaborative HIV Research, Kampala, March 2008. <http://hivforum.org/projects/Male%20Circ.html>

46 The greater vulnerability of uncircumcised men to HIV infection is believed to be associated, in part, with the concentration of Langerhans cells in the mucosal tissue on the underside of the foreskin, and also due to the lack of keratinised tissue on the underside of the foreskin. Thus circumcision methods that remove less of the foreskin, leaving some of this mucosal surface intact, may not maximise the potential of circumcision to reduce the risk of HIV infection.

no need for a return visit to the clinic. A wide range of products is available. The performance of a necrosing clamp in a mass adult male circumcision programme has not been evaluated.

Any device developed for adult use will require field testing. WHO is due to convene a meeting in late 2008 among regulators, policymakers, clinicians and programme managers to achieve consensus on the minimum testing requirements for male circumcision devices.

Further device development opportunities have been analysed by PA Consulting Group<sup>47</sup> and by Battelle<sup>48</sup>. An ideal device would have the following features, according to Reade Harpham of Battelle:

- Protective of the glans penis.
- Positions the foreskin for removal and provides a guide for tissue removal, while controlling the amount of tissue removed.
- Results in minimal bleeding, a low adverse event rate and an acceptable cosmetic result.
- Easy to train, easy to use: no use of scalpel, fast operation, guided procedure suitable for lower cadre staff, consistent results.
- Sterile, disposable and auto-destructing, with no potential for re-use.
- Cheap, one size fits all, no electricity required.

Battelle's review of currently available devices concluded that none of the current products met all the criteria of an ideal device, and there is a lack of independent evaluation of manufacturer performance claims. Further field research is required to define the most important functions and features of devices, to evaluate existing devices and to identify alternative methods for wound closure.

Modelling by the Clinton Foundation estimates that demand for male circumcision could lie between 22.7 million and 53.1 million circumcisions among HIV-negative males in sub-Saharan Africa, with uptake dependent on the method used, cultural acceptability and the proportion of the cost to be met by the patient<sup>49</sup>.

Other technologies and products are also likely to be required when scaling up male circumcision provision:

- Needle-free anaesthetic that is cheap, easy to administer, stable in tropical climates. Topical anaesthesia, which avoids needles and would thus be useful, is still untested and the ideal topical agent undefined<sup>50</sup>.
- Pre-packaged consumables kit for each circumcision would help manage the supply

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47 Dan Walsh, John Gola. Circumcision – device solutions. Presentation at: Meeting the demand for male circumcision: an assessment of what is needed. Forum for Collaborative HIV Research, Kampala, March 2008.

48 R Reade Harpham. Landscape of MC devices. Presentation at: Meeting the demand for male circumcision: an assessment of what is needed. Forum for Collaborative HIV Research, Kampala, March 2008.

49 Jessica Fast. Estimating demand for male circumcision services. Presentation at: Meeting the demand for male circumcision: an assessment of what is needed. Forum for Collaborative HIV Research, Kampala, March 2008.

50 Kristin Chrouser, Harshad Sanghvi. Presentation at: Meeting the demand for male circumcision: an assessment of what is needed. Forum for Collaborative HIV Research, Kampala, March 2008.

chain: the current consumables required comprise at least eight separate items, any one of which could go out of stock at hospital, programme or national level overnight<sup>51</sup>. An expanded version of this might provide all the items needed to offer safe, high-quality circumcision, and would also include instruments and infection control supplies, simplifying the supply chain management.

- Wound dressing that encourages healing, possibly impregnated, that can be stored without deterioration in hot climates.

### 3.4.3 Future research questions

Many questions remain about the implementation and impact of circumcision.

One of the chief unknowns is the extent to which risk compensation might affect the population-level efficacy of circumcision. In two of the three randomised trials conducted to date there has been no strong evidence of risk compensation in circumcised men, but in the Orange Farm study circumcised men reported significantly greater numbers of sexual partners than the control group 21 months after circumcision<sup>52</sup>.

Unpublished modelling by Timothy Hallett of Imperial College, London, highlights the wide confidence intervals for efficacy seen in the three randomised studies, and the extent to which efficacy could be undermined if risk compensation occurs<sup>53</sup>. But modelling based on the Orange Farm data suggests that if the protective effect of circumcision is higher than 63%, condom use could fall to negligible levels without a negative impact on HIV prevalence among men over 20 years<sup>54</sup>.

Acceptability of circumcision may vary between countries and ethnic groups, and also between risk populations. More research will be needed to determine the acceptability of circumcision across different settings.

More comprehensive data on safety are also needed, as high rates of complications have been seen, both in settings where male circumcision is carried out by traditional healers as an initiation rite for young men and also in the formal health care system<sup>55</sup>. Given the shortage of health care workers, who should carry out the operation, does this have implications for the type of circumcision carried out, what are the logistical requirements and costs for different operations, and what staff training will be needed?

The safety results in HIV-positive men reported from the Rakai study raise another set of implementation questions: in settings where there is a high level of stigma attached to HIV infection, will it be possible to limit demand for circumcision to HIV-negative men, and what are the community education needs if men are circumcised irrespective of HIV status? The Rakai data do not address the speed of wound healing or rate of

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51 Steve Gesuale. Addressing the MC supply issue. Presentation at: Meeting the demand for male circumcision: an assessment of what is needed. Forum for Collaborative HIV Research, Kampala, March 2008.

52 Auvert B et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial, PLoS Med 2(11):e298, 2005.

53 Timothy Hallett. Oral presentation. HIV Implementers' meeting, Kigali, Rwanda, June 2007.

54 Mesesan K et al. The potential benefits of expanded male circumcision programs in Africa: predicting the population-level impact on heterosexual HIV transmission in Soweto. Sixteenth International AIDS Conference, Toronto, abstract TUAC0203, 2006.

55 Bailey RC, Egesah O, Rosenberg S. Male circumcision for HIV prevention: Complications in clinical and traditional settings in Bungoma, Kenya. Bull WHO 86(9):669-677. 2008

complications in men with CD4 cell counts below 350 cells/mm<sup>3</sup>, who are likely to be more infectious and may have slower wound healing<sup>56</sup>.

The duration of effect is also unknown. The randomised studies followed participants for two years and we now have evidence of continuing, or perhaps even increasing, protection from months 24-42 (Kisumu trial). Still, questions persist over circumcision's protective effect over time, especially in individuals with a high rate of partner change.

Questions of scale and targeting also need to be explored through operational research. Should programmes aim for:

- Routine offer of circumcision at birth?
- Routine offer of circumcision for male attendees at sexually transmitted infection clinics?
- Circumcision on demand, promoted through social marketing, possibly with a cost recovery element in some countries?
- Circumcision of men who have sex with men (MSM)? There is limited evidence about the impact of circumcision on HIV acquisition in MSM. An Australian study showed no effect of circumcision status on the risk of acquiring HIV among an incidence cohort of gay men recruited since 2001<sup>57</sup>, while a meta-analysis of studies looking at the risk of HIV acquisition in men who have sex with men did not find a reduction in risk associated with being circumcised (although an analysis limited to studies carried out before the introduction of antiretroviral therapy found a statistically significant 53% reduction in risk among men who were circumcised)<sup>58</sup>.

Other programmatic considerations include:

- What are the most effective strategies for counselling pre- and post-surgery to maintain, or adopt, safer sex behaviours?
- Given the lack of basic surgical services throughout most HIV-endemic areas, should a major investment be made in scaling up a single surgical service? Or should male circumcision be scaled up in the context of conjoint services for obstructed labour, appendectomies, and trauma services?

### **3.5 Microbicides**

A topical microbicide that can be used to provide protection from HIV infection is a major area of research-related investment. Although candidate microbicides recently tested in Phase II and Phase III trials failed to show protective effect, and although in one case there were indications of potential harm, two candidate products are still in late-stage trials and 12 others are in earlier stages of clinical testing. These include several products derived from antiviral compounds first developed as HIV therapeutics. Rectal microbicides

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56 Kigozi G et al. The safety of adult male circumcision in HIV-infected and uninfected men in Rakai, Uganda. Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract WEAC101, Sydney, 2007.

57 Templeton DJ et al. Circumcision status and risk of HIV seroconversion in the HIM cohort of homosexually active men in Sydney. Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract WEAC103, Sydney, 2007.

58 Millett G et al. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. *Journal of the American Medical Association* 300(14):1674-1684, 2008.



are also being developed, but are in very early development. Thus, unless otherwise stated, the study results discussed in this section refer to vaginal microbicides.

There are approximately 50 candidate compounds in the preclinical portion of the microbicide pipeline. Decisions about how best to evaluate them and select only the most plausible candidates for advancement are relentlessly challenging. The major challenges in the clinical part of the microbicide pipeline have to do with trial design, the logistics of conducting and analysing trials, and trial site capacity. Many of these issues also plague HIV vaccine research and development. What is specific for microbicide trials is the need to ensure consistent, correct, and validated use of the product being tested, since adherence to use is what determines whether or not the test product is truly effective.

### 3.5.1 How they work

Various mechanisms of action are being explored in the microbicide development process. These include strategies to disable HIV before it can enter host cells, strengthening the body's natural defences against viral entry, creating a physical barrier between host target cells and virus, interfering at various steps in viral transmission, and preventing HIV from reproducing itself and spreading to other host cells. It is these mechanisms of action that define the classes of microbicides discussed below.

**Surfactants** disable virus by damaging surface membranes or envelopes. Alternatively referred to as “surface-active” or “membrane-disruptive”, these agents were first used in approved and commercially available spermicides and were later found *in vitro* to disrupt not only sperm but some bacteria and, later, HIV. Thus they were seen by earlier developers as a logical point of departure for development as microbicides that would have broad-spectrum efficacy against not only HIV but other sexually-transmitted pathogens, as well as offering potential contraceptive efficacy in some cases. This class<sup>59</sup> comprised the earliest microbicides to be developed and included the already marketed surfactant nonoxynol-9 (N-9) formulated in a sponge, a film, and the COL-1492 (Advantage-S®) gel and, later, Savvy (C31G), a gel containing another surfactant. All eventually reached late-stage clinical testing.

**Acid-buffering agents**, also referred to as vaginal defence enhancers, work primarily by maintaining the normal acidic environment of the vagina so that sperm and many STD pathogens are less likely to survive. The primary exemplar of this class is BufferGel®, now in an ongoing Phase II/IIb study (HPTN 035) with 0.5% PRO 2000 (*see below*). Another product, Acidform™/Amphora™, is also being studied, including its potential as a vehicle for other active agents.

**Non-specific entry inhibitors** interfere with attachment of HIV or its engagement with healthy host cells, ideally before the membranes of the two cell types can bind or fuse. Generally referred to as the “second generation” of microbicides, this class comprises sulphated or sulfonated negatively-charged polymers, or polyanions, presumed to work similarly at the binding, fusion, and entry stages of the viral life cycle.<sup>60</sup> This class includes Carraguard®, cellulose sulphate/CS (trade name UsherCell®), PRO 2000, and VivaGel®.

59 Abdool Karim S. XVII International AIDS Conference, Mexico City. Presentation, Panel on the future of microbicides: from vaginal ART to PrEP. 7 August 2008.

60 Scordi-Bello IA, Mosoian A, He C, Chen Y, et al. Candidate sulfonated and sulfated topical microbicides: comparison of anti-human immunodeficiency virus activities and mechanisms of action. *Antimicrobial Agents Chemotherapy* 49(9):3607-3615, September 2005.

**Specific entry/fusion inhibitors.** This candidate class consists primarily of compounds licensed to the International Partnership for Microbicides (IPM) by pharmaceutical companies, all in very early stages of preclinical development.

**Replication inhibitors** are formulations of antiretroviral (ARV) drugs that act post-fusion to suppress HIV replication in host cells, in the case of microbicides either in the vagina or rectum. The members of this class that have reached clinical testing are dapivirine (TMC-120), MIV 150, tenofovir, and UC-781.

**Combination microbicides.** An increasing number of approaches are being explored whose intent is to combine multiple mechanisms of action or modes of delivery so as to interrupt HIV infection at different points in the viral life cycle, prevent other viral or bacterial infections, or to block conception.

### 3.5.2 The “first generation” of microbicides: surfactants

**COL-1492 and Savvy.** The two members of the surfactant class that reached effectiveness testing were COL-1492 and Savvy. Neither proved successful, however, for different reasons. Results from a four-year trial of COL-1492 found that it had no protective effect on HIV-1 and showed possible evidence of harm in high-frequency use<sup>61</sup>. Testing of other N-9 formulations determined similarly and also found no efficacy of these formulations against other sexually-transmitted pathogens.<sup>62</sup> The Savvy trial was halted in 2006 when preliminary data showed no statistically significant differences in HIV infection rates between women using the product and those using comparison placebo gel.<sup>63</sup>

### 3.5.3 The “second-generation” of microbicides: non-specific entry inhibitors

Three members of this class have advanced into effectiveness trials: Carraguard®, cellulose sulphate (CS or UsherCell™), and PRO 2000. The trials of Carraguard and CS have ended; the PRO 2000 effectiveness trials continue.

**Carraguard.** The effectiveness trial of Carraguard® gel, a seaweed derivative, was the first microbicide effectiveness trial to be completed since 2000. This 6,202-person Phase 3 randomised, double-blind study conducted at three sites in South Africa found no significant difference in protective effect between Carraguard® and placebo.<sup>64</sup> Conclusions about the safety of Carraguard® in very frequent use were constrained by the substantial discrepancy between self-reported adherence to product use and the biological measures of adherence that were specifically developed for this study.<sup>65</sup> Subgroup analysis may be able to determine whether efficacy can be demonstrated in individuals with higher levels of adherence, but will not change the overall finding of lack of effectiveness.

**Cellulose sulphate** (also known as CS and by its trade name, *UsherCell*) is a high-molecular-weight polymer gel that showed *in vitro* activity against HIV and other sexually

61 Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomized controlled trial. *Lancet* 360(9338):971-977, 2002.

62 Marais D, Carrara H, Kay P, Ramjee G, et al. The impact of the use of COL-1492, a nonoxynol-9 vaginal gel, on the presence of cervical human papillomavirus in female sex workers. *Virus Research* 121(2):220-222, November 2006.

63 Feldblum PJ, Adeiga A, Bakare R, Wevill S, Lendvay A, et al. (2008) SAVVY Vaginal Gel (C31G) for prevention of HIV infection: a randomized controlled trial in Nigeria. *PLoS ONE* 3(1): e1474. doi:10.1371/journal.pone.0001474

64 Carraguard microbicide safe but not effective <http://www.aidsmap.com/en/news/83D932E5-6D7B-4E45-AE95-17465D5FAAB8.asp>

65 Johansson E. Results of the Phase III Carraguard trial. Plenary, Microbicides 2008 Conference, Delhi. February 2008.

transmitted infections, and has been tested as a contraceptive.<sup>66</sup> The gel gave no indication of potential for harm in preclinical testing and 10 earlier human safety studies; in two contraceptive trials, cellulose sulphate had showed no evidence of harm and appeared acceptable to users.<sup>67</sup>

However, the Phase 3 effectiveness trials being conducted by CONRAD in Benin, India, South Africa, and Uganda were terminated in January 2007 following Data Safety Monitoring Board interim analysis of data which pointed to evidence of harm. A parallel Phase 3 study being conducted by Family Health International (FHI) in Nigeria did not find similarly but was also halted as a precautionary measure.

Further analysis of the study data showed that the difference in infection rates between the active and placebo arms as manifested in numbers of seroconversions was not statistically significant.<sup>68, 69</sup> Recent *in vitro* analysis using a new assay found that cellulose sulphate displayed unexpected tissue toxicity, apparently due to selective destruction of a protein that maintains host-cell barriers against HIV entry<sup>70</sup>. Further tests, using new assays and samples from multiple sites, are being carried out to determine what might explain the finding of harm, given the lack of such evidence in preclinical and early clinical testing.

**PRO 2000** is a naphthalene sulfonate polymer active *in vitro* against HIV-1 and -2, herpes, chlamydia, and gonorrhoea, that functions as an entry inhibitor. It is being tested in a US National Institutes of Health Phase II/IIb, four-arm, multi-site, randomised controlled trial comparing 0.5% PRO 2000/5 Gel (P) with BufferGel®, a placebo gel, and with no gel. The study, designated as HPTN 035, has completed recruitment in sexually active HIV-uninfected women from Malawi, South Africa, the United States, Zambia, and Zimbabwe. HPTN 035 has been reviewed by its DSMB on several occasions, no concerns have arisen, and the study is expected to report results in early 2009. The UK's Medical Research Council is also sponsoring an effectiveness trial of PRO 2000 (MDP 301) in Tanzania, Uganda, Zambia, and Zimbabwe. This study was designed to study two concentrations of PRO 2000, 0.5% and 2%; however, an interim DSMB data analysis recommended discontinuing the higher-potency formulation on grounds of futility, and that study arm was dropped<sup>71</sup>. The first results from the PRO 2000 trials are expected in early 2009. Safety studies of PRO 2000 as a rectal microbicide in men who have sex with men are due to begin in 2008. The study is being sponsored by MDP.

### 3.5.4 The “next generation” of microbicides: specific inhibitors

The next generation of microbicides comprises compounds that intervene at specific

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66 Mauck CK, Freziers RG, Walsh TL, et al. Noncomparative contraceptive efficacy of cellulose sulfate gel. *Obstetrics & Gynecology* 2008;111:739-746.

67 National Institutes of Health. AIDSinfo. 19 September 2007. [http://www.aidsinfo.nih.gov/DrugsNew/DrugDetailT.asp?int\\_id=409](http://www.aidsinfo.nih.gov/DrugsNew/DrugDetailT.asp?int_id=409)

68 Van Damme L, Govinden R, Mirembe FM, Guedou S, et al. Lack of effectiveness of cellulose sulphate gel for the prevention of vaginal HIV transmission. *N. Engl. J. Med.* July 31, 2008; 359(5):463-472.

69 Halpern V et al. Effectiveness of cellulose sulfate gel for prevention of HIV: results of the phase III trial in Nigeria. Fourth International AIDS Society Conference on HIV Treatment and Pathogenesis, Sydney, Abstract WESS302, 2007.

70 Mesquita PMMO. Disruption of the epithelial barrier by cellulose sulfate: development of a model to assess microbicide safety. Microbicides 2008 Conference, Delhi, Abstract AO10-415, 2008.

71 Microbicide PRO 2000: higher dose abandoned, lower dose studies continue. February 18, 2008. <http://www.aidsmap.com/en/news/B260FF22-293C-46F4-A947-307E0268BE02.asp>

points in the HIV life cycle and its interactions with host cells. These compounds are largely derived from drugs or compounds developed as antiretroviral therapies and tend to be small molecules, unlike the large-molecule non-specific candidates that dominated the second generation of microbicides. At present, the leading members of this next-generation class are replication inhibitors, which act to suppress the ability of HIV to reproduce itself in the cells of the host vagina or rectum.

### ***Replication inhibitors***

The microbicide candidates in this class that have reached clinical testing are the non-nucleoside RTIs (NNRTI) dapivirine (TMC 120) and UC-781, and tenofovir, a nucleotide analog RTI (NtRTI). Each is at a different stage of development.

*Tenofovir*, developed by Gilead Sciences, is a widely used antiretroviral drug. It has a good safety profile and long half-life as an oral product, has shown protection in multiple animal challenge studies, and has a high barrier for drug resistance. It has been licensed by both CONRAD and IPM for further development in a gel formulation for topical application as a vaginal microbicide.

Tenofovir vaginal gel is being tested in two trials in a comparison with oral dosing of tenofovir. In the recent HPTN 059 phase II safety trial in 200 sexually active, HIV-negative women in India and the United States, the gel was found safe and highly acceptable to participants. CAPRISA 004, an ongoing phase IIb proof-of-concept study testing coitally-dependent use of 1% tenofovir gel in 1,250 women in South Africa, is targeted for completion in 2010. Finally, the Microbicide Trials Network is planning the MTN 003 VOICE (Vaginal and Oral Intervention to Control the Epidemic) study that will compare tenofovir 1% vaginal gel with oral tenofovir (Viread™), and the tenofovir-emtricitabine combination Truvada™ as oral pre-exposure prophylaxis. This five-arm trial will enrol 4,200 women at 10 sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe; estimated start date is early 2009 with completion in 2011/2012.

*Dapivirine (TMC120)*, an experimental drug developed by Tibotec/Virco, had been abandoned as a potential second-line therapy due to its poor absorption when taken orally. A potent drug of apparently low toxicity, it was licensed to IPM for development both as a gel and a drug for diffusion via a slow-release vaginal ring. IPM has laid out a sequence of 23 studies of the gel and the ring; acceptability, feasibility, pharmacokinetics, and safety have been the subject of seven studies completed to date in Belgium and Southern Africa<sup>72</sup>. A Phase 3 study of dapivirine gel (IPM 009) is being planned to follow a series of safety studies, with an estimated 2010 start and possible completion by 2012/13. Timing of the ring trials depends on preliminary safety and formulation studies<sup>73</sup>.

*UC-781* was licensed to CONRAD in 2006 from Biosyn/Cellegy for development and public-sector marketing. A tight-binding NNRTI with high potency alone and in drug combinations, it appears to have low toxicity. Safety studies are underway with CDC in Thailand and Atlanta, USA. A male tolerance study has been initiated at the California Family Health Council in Los Angeles, and a PK study has been completed at the University of Pittsburgh. UC-781 is also being studied at the University of California, Los Angeles, in the first series of studies to test

72 Alliance for Microbicide Development. Microbicide candidates in completed, planned, and funded trials; summary as of August 2008. Silver Spring, MD, USA. [http://www.microbicide.org/cs/microbicide\\_pipeline](http://www.microbicide.org/cs/microbicide_pipeline)

73 Cairns G. Microbicides 2008: The second generation is on its way. February 28, 2008. <http://www.aidsmap.com/en/news/969360D8-96E6-4E85-873F-654BB7E652DA.asp>

rectal microbicides in human subjects; these trials are testing 1% and 2.5% UC-781 in gel and are using a new biopsy assay that could provide early insights into the compound's toxicity and potential efficacy.

### ***Specific entry inhibitors***

*Maraviroc (Celsentri/Selzentry™)* is a newly-approved CCR5 co-receptor blocker that does not share a resistance profile with any other approved antiretroviral drug. It was licensed in early 2008 from Pfizer to the IPM and is in preclinical assessment; animal dosing studies are ongoing.

This microbicide candidate class contains other CCR5 antagonists – PSC-RANTES, aplaviroc, and Merck-167, 872, and 882, also licensed to the International Partnership for Microbicides; all are in early preclinical development. Highly potent ARVs that could be effective even when applied topically days before coitus, CCR5 antagonists can bind to CCR5 receptors for up to five days, offering potential for a longer-acting microbicide. The RANTES analogue PSC-RANTES has been shown to protect against transmission in a macaque model, but formulation and high manufacturing costs remain constraints and various strategies are being pursued to address them<sup>74</sup>. This class also includes the gp120 binder BMS793 and the gp41 binder peptide L'644 licensed to IPM by Bristol-Myers-Squibb and Merck, respectively.

### **3.5.5 Enhancers of natural defences**

Until recently, only one member of this class—BufferGel™—had advanced significantly in clinical testing. With time, the bacterial therapeutics company Osel, NIH researchers, and a few university groups have pursued strategies for genetically engineering naturally-occurring vaginal bacteria to introduce and/or produce microbicides; plant-based production approaches are also being pursued. The candidate “enhancers” being explored include cyanovirin-N and RANTES derivatives. Related research has focused on other ways of mobilizing vaginal microflora toward HIV prophylactic and therapeutic objectives<sup>75</sup>.

### **3.5.6 Combination microbicides**

Combinations of different antiretrovirals, diaphragms pre-loaded with a microbicide, and intravaginal rings releasing both antiviral and contraceptive agents are approaches under consideration. IPM is considering a possible combination of dapivirine and maraviroc, in gel and/or ring, and CONRAD is exploring the potential of combining UC-781 and tenofovir. The Population Council is also contemplating possibilities for combining Carraguard essentially as a vehicle for MIV-150, an NNRTI licensed in from Medivir.

There is also revived interest in pursuing approaches that address other non-HIV sexually transmitted infections and the ongoing need for better contraceptive options, particularly those that might provide dual protection from infection and conception when that is desired. The potency of ARV-derived microbicides is compelling but their specificity excludes the possibility of activity against other STIs or other benefits for vaginal health or contraception.

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74 Cairns G. Microbicides 2008: Third-generation microbicides might act as ‘bacterial vaccine’. AIDSmap, 4 March 2008.

75 Cairns G, Differding V. AIDSmap, 5 February 2008. <http://www.aidsmap.com/en/news/C20869A7-FB55-4C87-A7B2-9E9A047E6466.asp>

The barrier methods discussed later in this document respond to some of this concern and the entire concept of combination strategies is receiving renewed attention. As just one example, CONRAD is pursuing the concept of a ring that would slow-release an antiretroviral and a compound with contraceptive activity.

### **3.5.7 Rectal microbicides**

Translation of research on vaginal microbicides to rectal microbicides is not straightforward, primarily because of significant physiological differences between the vaginal and rectal compartments. There are major issues around sensitivity deriving from differences in tissue structure, major challenges with respect to the amount of surface area that must be covered, and a range of questions related to the very different architecture and associated biology of the vagina and anorectal tract. However, even though this is a relatively new area of exploration, support is increasing, interesting basic and translational research is proceeding, and clinical research has begun. The latter includes Phase 1 safety and tolerability studies of several products already developed as vaginal microbicides that are under way or planned, including PRO 2000, UC-781, and VivaGel™.

### **3.5.8 Future research questions**

A number of critical dilemmas in the basic science persist:

- Is it cell-free or cell-associated virus that is being transmitted, and are there differences in activity of some microbicides against each of these?
- Which are the most relevant target cells and receptors for HIV infection in the vagina and rectum, and what are the roles of seminal plasma, cervical vaginal fluid, and vaginal flora, all of which will, in various ways, affect microbicide efficacy?

Other questions include:

- What is the utility of a microbicide that protects only against HIV?
- Are microbicides containing a combination of products with different modes of action more effective?
- How can microbicides be developed that are not dependent on administration shortly before sexual intercourse? Longer-lasting formulations using antiretroviral drugs with longer periods of effect, such as CCR5 inhibitors, or novel dispensing methods such as a vaginal or cervical ring are examples of the approaches already being considered.

The growing prominence of ARV-derived topical microbicides presents an additional array of issues.

Systemic absorption–leakage of the drug from the vagina into the bloodstream– is a crucial question for ARV-containing microbicides. The biggest safety concern surrounding these compounds is whether women using them who are HIV-positive but undiagnosed, or who acquire HIV despite using them, could develop drug resistance. This has implications for potential subsequent transmission of drug-resistant HIV, and for the future treatment of those who become infected despite microbicide use.

There is some evidence of tissue accumulation of dapivirine<sup>76</sup>, and very low-level systemic absorption of tenofovir<sup>77</sup>, but the longer-term implications of these observations are unknown.

Current studies are designed to evaluate the potential for the development of HIV resistance in trial participants who use these ARV -based products. The MTN 015 trial, an HIV seroconverter study, will evaluate the possible outcome over time of HIV seroconverters who have contact with ARV-based products. The MTN 016 trial is a first-of-its-kind registry of women who become pregnant while participating in an HIV prevention trial of either a microbicide or an oral drug, which will help determine any effects of early exposure to these products on foetal and/or neonatal development.

### **3.6 Other female-initiated barrier methods**

Adaptation of the diaphragm and other cervical barriers for HIV prevention has been a goal<sup>78</sup>. However the first major study of the diaphragm failed to show benefit. The MIRA study randomised around 5,000 women in Zimbabwe and South Africa to use a diaphragm and lubricant, or lubricant alone. The study found no significant difference in HIV incidence between the arms, even though condom use in the diaphragm arm was significant lower. The study was not adequately powered to show whether the diaphragm reduced the risk of infection in women who did not use condoms consistently<sup>79</sup>. Consistent use of the diaphragm was reported by around 70% of women.

A study of the effectiveness of the diaphragm in preventing sexually transmitted infections is still underway in Madagascar.

However, not all diaphragms are of the same design, and different devices may have differing acceptability. A range of products are now being developed, some designed to be used with a microbicide:

- BufferGel Duet: the Duet is a sombrero-shaped diaphragm which, when lubricated with microbicide, should ensure coverage of the microbicide in the cervix and the vagina<sup>80</sup>.
- SILCS diaphragm (PATH) is a single-size cervical barrier, designed to provide the same effectiveness as standard diaphragm, while being easier to supply and provide. The pivotal study that will lead to FDA approval as a contraceptive is underway in the US, with results expected by 2010. It is also being evaluated as a microbicide delivery vehicle for added protection from STIs. PATH is seeking commercialisation partners to plan for product introduction in developed and developing countries.

76 Nel A. Pharmacokinetic assessment of an anti-HIV dapivirine vaginal microbicide gel (Gel-002). Microbicides 2008 Conference, Delhi, abstract BO10-563, 2008.

77 Schwartz J et al. Preliminary results from a pharmacokinetic study of the candidate vaginal microbicide agent 1% tenofovir gel. Microbicides 2008 Conference, Delhi, abstract BO11-610, 2008.

78 Moench, Chipato and Padian, Preventing disease by protecting the cervix: the unexplored potential barrier devices. 2001, AIDS 15:1595-1602

79 Padian NS et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. The Lancet 370(9583):251-61, 2007.

80 <http://www.reprotect.com/products.shtml>

### 3.6.1 Female condoms

Despite the overwhelming need for improved options for dual protection from pregnancy and STIs, the female condom still has poor availability 14 years after product approval, chiefly due to price: in 2006 it cost an estimated 27 times more than the male condom. To achieve a major price reduction, use of the female condom would need to rise from 14 million in 2005 to at least 300 million worldwide<sup>81</sup>. A number of country programmes are expanding usage of the current female condom products, and UNFPA is developing a large-scale project with a number of partners.

Two products are currently available:

- Currently procurement is focused on the FDA-approved nitrile FC2 condom, which replaces the polyurethane product approved in 1993.
- The latex VA Condom Feminine is approved in Europe, South Africa, Indonesia and Brazil, and is available through female condom programmes in some African countries. It has a V-shaped external ring and a pre-formed pouch containing an anchoring sponge in the tip.

Current product availability is limited, UNFPA notes, and amending clinical trial requirements and streamlining the regulatory approval process in the United States may help bring innovative female condom products to market.

Other products in the pipeline:

- PATH has developed the Woman's Condom (WC) with input from couples from four countries to ensure improved ease-of-use and acceptability. Results from a 3-way study in South Africa comparing acceptability of second-generation female condom designs (including the WC) are scheduled for release later this year. PATH is seeking funding for technology transfer to a manufacturer to ensure product supply and for the clinical studies needed for product testing, and if successful, approval, registration and to ensure long-term product supply.
- The Silk Parasol Female Panty condom is, as its name implies, a female condom built into a one-use garment designed to avoid condom slippage and application difficulties around the time of coitus.
- Belgian Female Condom, a latex device being developed by the Catholic University of Louvain.

### 3.6.2 Future research questions

Future research questions for female-initiated barrier methods include:

- The role of the cervix and the upper genital tract in HIV acquisition. The cervix has a higher density of HIV target cells than the vagina – what proportion of HIV infections occur at this site<sup>82 83</sup>? What fraction of infections in females occur by alternative sexual routes, particularly anal intercourse?

81 Catherine Hankins. Debate on female barrier methods – why they may not be effective at this rate (presentation). Biomedical interventions for HIV prevention working group, Washington DC, September 2006.

82 Ariane vander Straten, Nancy Padian. Female controlled physical barrier methods (presentation). Biomedical interventions for HIV prevention working group, Washington DC, September 2006.

83 See also <http://www.cervicalbarriers.org/information/preventing.cfm>



- The effects of cervical barriers on innate vaginal immunity.
- The extent to which different types of barriers – including the female condom – protect against HIV transmission.
- Is the diaphragm as protective as the male condom? To what extent can women use it autonomously?
- Might a diaphragm and microbicide used together be more effective than either product used alone?
- The acceptability of different products, to be tested in a variety of populations.
- How to measure adherence in barrier studies – could a computer chip that reacts to body temperature or pH provide an independent measure?
- How to increase demand for female-controlled barrier methods of HIV prevention.
- How to increase adherence to barrier methods of HIV prevention.

### **3.7 Antiretroviral prevention: Pre-exposure prophylaxis (PrEP)**

Pre-exposure prophylaxis (PrEP) is the use of antiretrovirals prior to exposure to HIV to prevent infection. PrEP is intended for use by people who may be at frequent risk for HIV. This includes high-risk behaviour groups such as commercial sex workers, injecting drug users, discordant couples, and people who have unsafe sex with a multiple partners (or whose partners have multiple partners). Currently, no antiretroviral is yet approved or in use as PrEP.

Much of the data on PrEP result from research conducted in monkeys. These have included studies examining the effects of single drugs, notably tenofovir (TDF, known in the US as *Viread*) in preventing infection with HIV and similar viruses in monkeys, as well as a recent trial examining the effects of combining tenofovir with emtricitabine (FTC). The combination of TDF and FTC is marketed as *Truvada*.

In general, these studies have demonstrated that PrEP can decrease the risk of infection<sup>84</sup><sup>85</sup><sup>86</sup>. However, they used different models for testing, such as different doses of virus and routes of viral inoculation and drug delivery, making comparisons across studies difficult.

The only human data to date, from a Family Health International study of tenofovir PrEP, show no serious safety concerns during an average of nine months' follow-up, but the study was inadequately powered to provide any evidence of efficacy<sup>87</sup>.

84 Tsai CC et al. Prevention of SIV infection in macaques by (R)-9-(2- phosphonylmethoxypropyl)adenine, *Science* 270: 1197-1199, 1995.

85 van Rompay KK et al. Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection, *J Infect Dis* 184: 429-438, 2001.

86 Garcia-Lerma JG et al. Prevention of rectal SHIV transmission on macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Medicine* 5(2):291-299. 2008.

87 Peterson L et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clin Trials*. 2007; 2(5):e27.

## Ongoing and Planned PrEP Trials as of August 2008<sup>88</sup>

Location	Sponsor/ Funder	Population (mode of exposure)	Intervention arms	PrEP strategy(ies) being tested	Status / Expected completion
United States	CDC	400 men who have sex with men (penile/rectal)	1	TDF	Fully enrolled – Ongoing/2009
Thailand	CDC	2,400 injecting drug users (parenteral)	1	Tenofovir disoproxil fumarate (TDF)	Fully enrolled
Botswana	CDC	1,800 heterosexual men and women (penile and vaginal)	1	TDF+emtricitabine (FTC) (switched from TDF Q1 2007)	Enrolling / 2010
Peru, Ecuador, US, additional sites TBD (iPrEX Study)	NIH, BMGF	3,000 men who have sex with men (penile/rectal)	1	TDF+FTC	Enrolling / 2010
Kenya, Uganda (Partners Study)	BMGF	3,900 serodiscordant couples (penile and vaginal)	2	TDF; TDF + FTC	Enrolling / 2012
Kenya, Malawi, South Africa, Tanzania (FEMPrEP)	FHI, USAID	3,900 high-risk women (vaginal)	1	TDF+FTC	Planning / 2012 Anticipated start Q3/2008
Malawi, South Africa, Uganda, Zambia, Zimbabwe (VOICE Study)	MTN, NIH	4,200 sexually active women (vaginal)	3	TDF; TDF+FTC; TDF gel	Planning / 2012 Anticipated start Q1/2009
BMGF – Bill & Melinda Gates Foundation CDC – US Centers for Disease Control FHI – Family Health International MTN – Microbicide Trials Network NIH – US National Institutes of Health USAID – United States Agency for International Development					

### 3.7.1 Premature halting of early studies

Despite the promise of this approach, clinical trials into PrEP have faced numerous difficulties over the past few years. Trials of tenofovir PrEP were prematurely halted at two sites, Cambodia and Cameroon, because activists were concerned about the study procedure and post-trial care. Tenofovir PrEP trials at two other sites were stopped on different grounds. In Nigeria, the site was not able to comply with the appropriate laboratory and clinical conditions needed for the safe conduct of the trial. In Malawi, government feared use of tenofovir for prevention would compromise its use for treatment. In Thailand, concerns were raised about provision of sterile needles, but the trial wasn't stopped.

In response to the controversies associated with these trials, the International AIDS Society convened a stakeholder consultation to address some of the ethical concerns related to PrEP research, in collaboration with the CDC, the National Institutes for Health, Family Health International, and the Gates Foundation. This has now become part of an

<sup>88</sup> Table reproduced with kind permission of AVAC; [http://prepwatch.org/pdf/Trials/PrEP\\_trials\\_table.pdf](http://prepwatch.org/pdf/Trials/PrEP_trials_table.pdf)

ongoing dialogue to ensure that future studies proceed with the support of local and international communities. Another response to the controversy surrounding these trials was the development of UNAIDS and WHO joint *Guidance on ethical considerations in biomedical HIV prevention trials*<sup>89</sup> and UNAIDS/AVAC *Good participatory practice guidelines*<sup>90</sup>.

### 3.7.2 Public health implications of PrEP

Researchers have noted the important public health potential of pre-exposure prophylaxis (PrEP) for HIV. If it proves effective, it may play an important role in limiting the spread of HIV in high-prevalence countries and protect those most vulnerable to HIV.

Even a partially effective PrEP strategy may prove cost-effective due to a reduction in the number of new HIV infections, although these will need to be balanced against the risks of reduced condom use and treatment-related toxicity<sup>91</sup>.

A study presented at a 2007 meeting looked at the potential of PrEP to avert new HIV infections in resource-limited settings<sup>92</sup>. Factors included in this model were the effectiveness of PrEP, the proportion of the population taking PrEP, the proportion of individuals who stopped taking PrEP, HIV drug resistance as a result of PrEP use, and the extent to which the use of PrEP led to an increase in sexual activity involving a risk of HIV transmission.

The most optimistic scenario, with PrEP being 90% effective, and taken by 75% of the population, would, the investigators calculated, lead to a 74% drop in new HIV infections over ten years. A more realistic scenario, however, with PrEP of 60% efficacy, would lead to a 25% drop in infections over the same time period.

When the model was modified to assume the same level of effectiveness, but use by only the most sexually active groups (16% of the population in the initial model), the percentage of HIV infections averted would drop by 29% if PrEP was 90% effective and only 7% if it was 60% effective. However because fewer people would have to receive PrEP the cost per infection averted in the 'optimistic' scenario would drop from \$6812 to \$638 for tenofovir alone and \$974 for tenofovir/FTC.

In terms of a possible disinhibiting effect on behaviour if PrEP were introduced, it was calculated that if the number of risky sexual encounters doubled, the number of infections would actually increase if PrEP was less than 50% effective.

### 3.7.3 Future research questions

The ongoing PrEP trials due to deliver results by the end of 2010, will provide the raw material for a substantial meta-analysis, but may leave a range of questions partially unanswered:

- How can effectiveness be maximised? Would the use of multiple drug classes in combination increase the effectiveness of PrEP?
- Is daily dosing necessary or can longer dosing intervals provide equivalent

89 UNAIDS/WHO. Guidance on ethical considerations in biomedical HIV prevention trials. 2007.

90 UNAIDS/AVAC. Good participatory practice guidelines for biomedical HIV prevention trials. 2007.

91 Grant R. Cost-effectiveness analysis of HIV chemoprophylaxis, 16th International AIDS Conference, Toronto, abstract ThLb0102, 2006.

92 Abbas U et al. Potential effect of ARV chemoprophylaxis on HIV-1 transmission in resource-poor settings, Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 32, 2007.

protection? Will other drugs with longer half-lives, such as elvucitabine<sup>93</sup>, facilitate longer dosing intervals more effectively? Can long-lasting depot or nanoformulations of drugs extend the dosing interval to weekly or even monthly dosing?

- Does episodic dosing (taking PrEP only around the time of an anticipated exposure) have a protective effect.
- How long does PrEP remain effective in a population? Is there a decline in adherence and an increase in resistance?
- What effect does taking PrEP have in individuals who acquire HIV infection? Do they develop resistance and do they transmit drug-resistant virus? What effect does PrEP have on HIV treatment response in these individuals?
- What effect does PrEP have on risk-taking – both among those who take it and the in wider community?
- What effect might an HIV-specific prophylaxis medication have on rates of STIs and pregnancy?
- Does FTC-containing PrEP protect against acquisition of drug-resistant virus in settings where the M184V mutation related to 3TC or FTC treatment is common and detectable viremia frequent among sexually active individuals?
- Should a a class of antiretroviral drug be reserved for use only as PrEP or in ARV-containing microbicides?
- How does PrEP compare with a topical microbicide containing tenofovir? The VOICE study will test this question in a study that may report in 2012.

A further strategy may be to combine different types of drugs to prevent infection, such as the use of topical microbicides with oral drug treatment to prevent infection.

### **3.8 Antiretroviral prevention: Post-exposure prophylaxis**

Post-exposure prophylaxis (PEP) is a course of anti-HIV medication that may block HIV infection after exposure. It appears to take HIV between one and three days to become established in the CD4 T-cells and lymph nodes after exposure<sup>94 95</sup>. It is thought that PEP acts during this time to prevent the virus from taking hold, thus preventing seroconversion in the person who was exposed.

PEP may have a particular niche in global HIV prevention if operational hurdles can be overcome, for example for use in cases of rape or following occupational exposure.

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93 Colucci et al reported that elvucitabine plasma levels persisted above the IC50 for 14 days after discontinuation, see: Colucci P et al. Efficacy and novel pharmacology of elvucitabine in a 7 day placebo controlled monotherapy study. 46th ICAAC, San Francisco, abstract H-1670d, 2006.

94 Abel, K., D. M. Rocke, B. Chohan, L. Fritts, and C. J. Miller. 2005. Temporal and anatomic relationship between virus replication and cytokine gene expression after vaginal simian immunodeficiency virus infection. *J. Virol.* 79:12164-12172.

95 Weiler, A. M., Q. Li, L. Duan, M. Kaizu, K. L. Weisgrau, T. C. Friedrich, M. R. Reynolds, A. T. Haase, and E. G. Rakasz. 2008. Genital ulcers facilitate rapid viral entry and dissemination following intravaginal inoculation with cell-associated SIVmac239. *J. Virol.* 82:4154-4158.

### 3.8.1 Effectiveness of post-exposure prophylaxis

A number of studies have examined the effectiveness of post-exposure prophylaxis (PEP) in animal models and in humans. Studies in humans have largely concentrated on occupational exposure, usually of healthcare workers. However, more recent findings have looked at infection rates following exposure through non-occupational means, such as unprotected sex. Almost all of the evidence on the effectiveness of PEP in humans comes from uncontrolled observational studies with relatively small sample sizes and inevitable selection biases.

Very few cases of HIV transmission have occurred after PEP, with only six reported transmissions worldwide in healthcare workers since 1997 after receiving PEP with two- or three-drug combinations<sup>96 97</sup>.

Studies of PEP after sexual exposure are limited. A Brazilian study of gay men found that fewer men became infected after sexual exposure if they took a course of PEP than did a similar group who chose not to take it<sup>98</sup>. Other studies have lacked control groups.

### 3.8.2 Drawbacks of post-exposure prophylaxis

- Low uptake due to lack of awareness or recognition of high-risk exposure.
- Poor adherence, chiefly due to drug side-effects: non-completion rates of up to 50% have been observed in health care worker studies<sup>99</sup>.
- Potential for lack of efficacy if there is a high prevalence of drug-resistant virus.

### 3.8.3 Guidelines for post-exposure prophylaxis

A number of organisations have published guidelines on the use of post-exposure prophylaxis<sup>100 101</sup>. Despite differences in degree of risk considered to be associated with different types of exposure and the choice of drugs for use in PEP, the guidelines generally concur in the need to begin PEP within 72 and preferably 24 hours after exposure for the best chances of success, and for treatment to last four weeks.

### 3.8.4 Future research questions

- How effective is PEP and what is its cost-effectiveness in different populations?
- How can access to PEP be expanded? What are the roles of community mobilisation and social marketing in increasing uptake of PEP?
- How long do PEP regimens need to be taken – is one month of treatment strictly

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96 Hawkins DA et al. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis, *J Infect* 43: 12-15, 2001.

97 Lot F et al. Occupational infections with HIV in France among health-care personnel, *Bull Epi Hebdom* 18: 69-70, 1999.

98 Praza Once Study Team. Behavioral impact, acceptability, and HIV incidence amongst homosexual men with access to postexposure prophylaxis, *J Infect* 43: 12-15, 2001.

99 Grime PR et al. Pan-Thames survey of occupational exposure to HIV and the use of post-exposure prophylaxis in 71 NHS trusts, *J Infect* 42: 27-32, 2001.

100 Fisher M et al. BASHH guideline: UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure, *Int J STD AIDS* 17: 81-92, 2006.

101 Smith DK et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States, *MMWR Recomm Rep* 54: 1-20, 2005.

necessary or could the duration of PEP be reduced?

- Which drugs are most suitable for use in PEP? Are three drugs always necessary? To what extent will national formularies and drug logistics in developing countries affect the scope of changes to PEP regimens, even if research shows that newer drugs might be better tolerated?
- How can the delivery of PEP be improved by health systems, and what are the current barriers to availability? How could service delivery innovations such as pre-packaging and pharmacy availability speed up and expand access to PEP in similar ways to those achieved for emergency contraception?

### **3.9 Antiretroviral prevention: Antiretroviral treatment of index partners**

Strong evidence suggests that antiretroviral treatment reduces HIV transmission by lowering viral load, and evidence from at least one study that current efforts to expand access to treatment in sub-Saharan have probably resulted in a major reduction in HIV transmission<sup>102</sup>. A three-year observational cohort study in Uganda of antiretroviral treatment coupled with intensive adherence support, behavioural counselling and partner testing led to an estimated 90% reduction in HIV transmission, CDC researchers calculated.

An ongoing study, HPTN 052, is evaluating two antiretroviral treatment strategies to determine whether earlier treatment in individuals with CD4 counts between 350 and 550 is more likely to reduce HIV transmission in serodiscordant couples than treatment initiated according to standard guidelines. Earlier treatment is defined as initiation of treatment as soon as an individual is enrolled in the study; initiation according to current standard guidelines means treatment if AIDS develops, or the CD4 count falls below 200. The study is powered to detect a 35% reduction in the rate of HIV transmission during a 5-year follow-up period. The study is recruiting in Brazil, India, Thailand, Malawi and Zimbabwe, and expected to report by 2013.

Modelling of the effects of antiretroviral treatment on HIV transmission suggests that antiretroviral therapy can reduce HIV incidence when:

- Treatment is introduced early in an epidemic, patient adherence is good, and HIV prevalence is low.
- Groups at high risk for transmission are targeted within low prevalence populations<sup>103</sup>.
- Levels of risk behaviour do not rise substantially (modelling suggests such an increase has its greatest effect on incidence in the early years, but relatively modest increases in risky behaviour might be enough to negate any effect of ART)

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102 Bunnell R et al. 3-year follow-up of sexual behavior and HIV transmission risk of persons taking ART in rural Uganda. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 29, 2008.

103 Anderson RM, Gupta S, May RM. Potential of community-wide chemotherapy or immunotherapy to control the spread of HIV-1. *Nature*. 1991;350:356-359.

on incidence)<sup>104</sup>.

- ART uptake is extensive.

### 3.9.1 Future research questions

Numerous questions remain unanswered about the impact of antiretroviral therapy on HIV transmission:

- Do any other factors increase the risk of HIV transmission in those with fully suppressed viral load, apart from sexually transmitted infections or inadequate drug penetration into the genital compartment?
- Are there differences in effects between antiretroviral regimens due to differences in penetration of various components into the genital tract? While nucleoside analogues such as tenofovir, FTC and 3TC have very good penetration, efavirenz and protease inhibitors have very poor penetration, achieving concentrations less than 10% of those in plasma<sup>105</sup>.
- Are there differences in effects of antiretroviral regimens on viral suppression in the rectum compared to the vagina or seminal tract?
- Urethritis, whether due to gonorrhoea or not, is associated with increased infectivity in men with undetectable plasma viral load, for example<sup>106</sup>. What effect will sexually transmitted infections have on infectivity against a background of widespread viral suppression at a population level?
- What effect will risk compensation have on HIV transmission? In San Francisco, for example, HIV incidence doubled between 1997 and 2001 as risk-taking behaviour increased, while rectal gonorrhoea incidence doubled between 1994 and 1999<sup>107</sup>. In Uganda the CDC HBAC programme found a return to baseline levels of unprotected sex after three years of antiretroviral treatment – but the annualised transmission risk remained below 0.5%, compared to 5% prior to treatment<sup>108</sup>.
- How will treatment failure affect HIV transmission, and what impact will this have in settings where viral load monitoring is not available, and treatment failure is thus slower to detect?

### 3.10 Prevention of mother-to-child transmission (PMTCT)

Pediatric HIV infection currently accounts for approximately 14% of all HIV related deaths<sup>109</sup>. Mother-to-child transmission remains a source of HIV transmission despite

104 S.M. Blower, H.B. Gershengorn and R.M. Grant. 2000. A tale of two futures: HIV and antiretroviral therapy in San Francisco. *Science* 287: 650 - 654.

105 Kashuba ADM, Dyer J, Eron JJ, Kramer LM, Raasch RH, Cohen MS. Antiretroviral-drug concentrations in semen: implications for sexual transmission of human immunodeficiency virus type 1. *Antimicrob Agents Chemother.* 1999;43:1817-1826.

106 Sadiq ST, Taylor S, Kaye S, et al. The effects of antiretroviral therapy on HIV-1 RNA loads in seminal plasma in HIV-positive patients with and without urethritis. *AIDS.* 2002;16:219-225.

107 San Francisco Department of Public Health. HIV Consensus Meeting Report Presentation. San Francisco, California. January 19, 2001.

108 Bunnell R et al. 3-year follow-up of sexual behavior and HIV transmission risk of persons taking ART in rural Uganda. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 29, 2008.

109 UNAIDS Epidemic Report 2007

substantial improvements in the effectiveness of prophylactic regimens over the past ten years. Although transmission can be reduced to <1-2%<sup>110</sup>, transmission rates remain unacceptably high largely due to operational barriers to implementation – in 2007, two-thirds of HIV-infected women in developing countries did not receive antiretroviral prophylaxis during pregnancy<sup>111</sup>. Prevention of mother to child HIV transmission contributes not only to the reduction of HIV transmission, but also to achievement of the Millenium Development Goal for child survival.

WHO defines four components that are crucial to a PMTCT programme:

1. Prevention of primary infection.
2. Prevention of unwanted pregnancy among HIV+ women.
3. Prevention of transmission to baby.
4. Care and support.

Without implementing effective interventions in all four areas, the pool of infected children will continue to rise, as will the pool of orphans and vulnerable children, many of whom are HIV-positive. Currently the third area, prevention of transmission to baby, is the chief focus of public health attention. A strikingly under-resourced area is voluntary contraception for HIV-positive women. Recent studies have shown that adding family planning to PMTCT programs is at least as, if not more, cost-effective as providing single dose NVP<sup>112 113</sup>.

### **3.10.1 Antiretroviral therapy and prophylaxis**

Current WHO guidelines recommend a short-course regimen ideally consisting of AZT for the mother from week 28 of pregnancy, single dose nevirapine at the onset of labour, and AZT/3TC for 7 days after delivery. The infant should also receive a single dose of nevirapine at delivery, and AZT/3TC for 7 days. Yet only about one quarter of women who receive any prophylaxis are receiving these recommended interventions.

Mothers with CD4 cell counts below 200 should receive HAART for life; women with CD4 counts less than 350 should be considered for similar lifelong antiretroviral therapy depending on resources available. In the absence of resources to estimate CD4 counts, HIV infected pregnant women with signs of advancing disease should equally be started on treatment as early in pregnancy as possible.

Less complex regimens are recommended where the health system cannot deliver this level of care, but even the delivery of single-dose nevirapine – the least effective regimen – has posed significant problems for health systems in sub-Saharan Africa. Detailed analysis of programme delivery in Zambia, for example, has shown that only one in three women diagnosed HIV-positive actually took nevirapine at delivery – but three times as many women were not offered, or did not consent to, HIV testing<sup>114</sup>.

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110 Volmink J. et al. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection Cochrane Database of Systematic Reviews Jan 24;(1):CD003510, 2007.

111 UNICEF, UNAIDS, WHO. Children and AIDS: Second stocktaking report. April 2008.

112 Reynolds HW et al..The value of contraception to prevent perinatal HIV transmission. Sex Transm Inf 33(6):350-6, 2006.

113 Sweat MD et al. Cost-effectiveness of nevirapine to prevent mother to child HIV transmission in eight African countries. AIDS 18: 1661-1671, 2004.

114 Stringer J et al. Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. AIDS 19 (12): 1309-1315, 2005.



Additionally, of major concern are data showing that after single-dose nevirapine, 19–75% of women<sup>115</sup> (and 33–87% of the minority of infants who become infected<sup>116</sup>) acquire resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs), a component of first-line ARV regimens, although recent longitudinal evidence suggests that this resistance decreases with time.

Combination therapy is therefore a critical component of PMTCT. The addition of maternal zidovudine/lamivudine was shown to significantly reduce detectable nevirapine resistance<sup>117</sup> and recent data have also shown that the addition of single-dose tenofovir/emtricitabine to short-course zidovudine and single-dose nevirapine could be a more effective strategy to reduce maternal nevirapine resistance<sup>118</sup>.

Infant dosing is also problematic, and the operational difficulties surrounding delivery of the drugs – particularly liquid nevirapine – led PATH to develop a nevirapine infant dose pouch containing an oral dosing syringe containing the correct nevirapine dose<sup>119</sup>.

No recent analysis of potential technological improvements to PMTCT programmes has been carried out<sup>120</sup>.

### 3.10.2 Infant feeding

It is estimated that 200,000 to 350,000 infants contract HIV via prolonged breastfeeding each year<sup>121</sup>. Yet in resource-poor areas lacking appropriate and nutritionally adequate breast milk substitutes and supplemental foods, breastfeeding for extended periods is widespread. Exclusive breastfeeding for the first six months of an infant's life has been documented to be protective against HIV transmission compared to partial or mixed breastfeeding<sup>122 123</sup>. This increased risk among mixed feeders is hypothesised to be due to the introduction of antigens and bacterial contaminants in food and water and the increased risk of mastitis in the mother<sup>124</sup>. Yet the overall risk of transmission if an infant is exclusively breastfed for six

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115 Eshleman SH et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS* 15(15):1951-7, 2001.

116 Eshleman SH et al. Resistance after single-dose nevirapine prophylaxis emerges in a high proportion of Malawian newborns. *AIDS* 19(18):2167-9, 2005.

117 McIntyre J et al. Addition of short course combivir (CBV) to single dose viramune (sdNVP) for the prevention of mother to child transmission (PMTCT) of HIV-1 can significantly decrease the subsequent development of maternal and paediatric NNRTI-resistant virus. The 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil, 24–27 July 2005 (Abstract TuFo0204).

118 Chi BH et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *The Lancet* 370(9600):1698-705, 2008.

119 See [http://www.path.org/projects/nevirapine\\_pouch.php](http://www.path.org/projects/nevirapine_pouch.php)

120 Personal communication with UNICEF, WHO, NIAID, Elisabeth Glaser Pediatric AIDS Foundation, ICAP.

121 De Cock K et al. Prevention of mother to child HIV transmission in resource poor countries: translating research into policy and practice. *JAMA* 283: 1175-1182, 2000.

122 Coutoudis A et al. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *AIDS* 15(3):379-87, 2001.

123 Iliff PJ et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS* 19(7):699-708, 2005.

124 Semba RD et al. Human immunodeficiency virus load in breast milk, mastitis, and mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 180(1):93-8, 1999.

months is only 4%<sup>125</sup>.

Thus, current WHO recommendations state that HIV-positive mothers should breastfeed exclusively for six months unless replacement-feeding is acceptable, feasible, affordable, sustainable and safe (AFASS), in which case avoidance of all breastfeeding is recommended. Cessation of breastfeeding should occur at six months only if a nutritionally adequate and safe diet is maintained<sup>126</sup>.

Despite these data showing that mixed feeding is high risk, it is widely practiced. Mixed feeding is the norm in most sub-Saharan African cultures, with approximately 70% of infants mixed fed during the first 3 months of life.

Current PMTCT strategies include counselling and support for safe infant feeding practices during antenatal and postnatal periods. Many health systems in developing countries, however, suffer severe staffing shortages, making comprehensive counselling on infant feeding a major challenge for most PMTCT programs.

A number of studies have examined the effects of **antiretroviral prophylaxis for infants during the breastfeeding period**. Several recent studies have also investigated the impact of infant prophylaxis during the breastfeeding period to reduce PMTCT of HIV. Observational<sup>127 128</sup> and randomised clinical trial<sup>129 130</sup> data have recently provided definite evidence that infant prophylaxis significantly reduces transmission. This effect diminishes over time in a breastfeeding population. The optimal duration of infant prophylaxis is unknown and given that early weaning may result in increased infant morbidity and mortality<sup>131</sup>, an evaluation of extended regimens is urgently needed. Studies are also ongoing or planned to assess the effects of maternal antiretroviral therapy on transmission through breastfeeding.

Research is also ongoing into methods for inactivation of HIV in breast-milk through heat treatment<sup>132</sup>, and into a nipple shield impregnated with sodium dodecyl sulphide that can inactivate HIV. The shield might also be used to deliver medicines<sup>133</sup>. The nipple shield was developed during a four-week collaboration at the 2008 International Design Development Summit, after participants were challenged to come up with an intervention to make breastfeeding safer.

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125 Coutoudis A et AL. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 189(12):2154-66, 2004.

126 WHO, UNAIDS, UNICEF, UNFPA. HIV and infant feeding: update. Based on the Technical Consultation held on behalf of the Inter-agency Task Team (IATT) on Prevention of HIV Infection in Pregnant Women, Mothers and their Infants, Geneva, Switzerland, 25-27 October 2006. [http://www.who.int/child\\_adolescent\\_health/documents/9789241595964/en/index.html](http://www.who.int/child_adolescent_health/documents/9789241595964/en/index.html)

127 Kilewo C et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr* 48(3):315-23, 2008.

128 Thior I et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA* 296(7):794-805, 2006

129 SWEN study team. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *The Lancet* 372(9635):300-13, 2008

130 Kumwenda NI et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *New England Journal of Medicine* 359. 2008

131 Kuhn L et al. Effects of early, abrupt weaning on HIV-free survival of children in Zambia. *N Engl J Med* 359(2):130-41, 2008.

132 Israel-Ballard K et al. Flash heat inactivation of HIV-1 in human milk. A potential method to reduce postnatal transmission in developing countries. *J Acquir Immune Defic Syndr* 45 (3): 318-323, 2007.

133 University of Cambridge press release, September 21 2008.

## **Future research questions**

Prevention of mother to child transmission is likely to remain one of the major areas of operational research for health services for many years to come. Some major questions include:

Preventing unwanted pregnancy:

- Which female-controlled contraceptives are most effective when used alongside HAART?

Maternal and infant testing:

- Reliability of rapid testing algorithms and the role of fourth generation antibody tests.
- Can a home testing and prophylaxis kit be developed to overcome the fact that many women deliver outside health care settings?
- A rapid, inexpensive HIV DNA test for infant HIV diagnosis is urgently needed (see section 5: Diagnostics).

Maternal prophylaxis and HAART:

- What is the safest, most effective and cost-effective HAART regimen for use in pregnant women? What are the long-term effects of HAART regimens on adverse birth outcomes and infant health?
- Is HAART more effective and cost-effective than short-course treatment? If so, in what circumstances?
- If HAART is used for all pregnant women, when is it safe to stop HAART?
- What is the impact of the development of resistance on maternal and infant responses to treatment?

Infant feeding:

- How do infant vs. maternal prophylaxis compare as affordable and sustainable strategies to reduce transmission through breastfeeding?
- What duration of infant prophylaxis is needed?
- Can a practical and affordable method of inactivating HIV in breast milk be developed, and can it be adopted easily in a wide range of settings?
- What water safety technology developments would make formula feeding safer?

Service integration:

- What is the best way of integrating family planning and PMTCT into health systems?
- How can health systems create better linkages between maternal health, sexual and reproductive health services, HIV care and child health services in ways that reduce mother to child transmission and also reduce maternal and child mortality?

### **3.11 Sexually transmitted infection treatment**

A wide range of sexually transmitted infections may increase the risk of HIV transmission and acquisition, either by recruiting vulnerable immune cells into the genital tract, by causing ulceration of the genitals that facilitates HIV entry or by up-regulating HIV replication in the genital tract.

In 1995 a randomised study of community-based treatment of sexually transmitted infections showed a 40% reduction in HIV incidence<sup>134</sup>.

But enthusiasm for population-level interventions waned after the results of the Rakai and Masaka studies in Uganda failed to replicate this result<sup>135 136</sup>. Subsequent analysis of the trials has led to the conclusion that sexually transmitted treatment is likely to have the greatest impact in epidemics where HIV prevalence is low, or amongst groups in generalised epidemics with high rates of STIs but low HIV prevalence, particularly adolescents.

A systematic review concluded that further community-based randomised trials that test a variety of STI control strategies are necessary<sup>137</sup>.

#### **3.11.1 HSV-2 suppression**

HSV-2 infection appears to double or triple the risk of HIV infection by creating lesions through which the virus can easily enter the body, and by causing immune activation that predisposes to HIV infection. It also increases HIV infectivity by activating HIV shedding in the genital tract.

Up to half of HIV infections in mature epidemics may be attributable to HSV-2<sup>138</sup>, and 80-90% of HIV-positive individuals, and 50% of HIV-negative women, are HSV-2 infected in sub-Saharan Africa<sup>139</sup>.

Given this strong epidemiological link there has been considerable interest in testing whether HSV-2 suppressive treatment in HIV-negative individuals can reduce their risk of HIV acquisition, and whether HSV-2 suppressive therapy also reduces HIV levels in genital fluids in women.

Results to date have been disappointing. Two large randomised studies failed to find any protective effect of daily acyclovir therapy in HIV-negative women or men who have sex with men, despite an observed reduction in genital ulcer disease in one study in acyclovir

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134 H Grosskurth, F Mosha, J Todd, et al. 1995. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *The Lancet* 346:530-536.

135 Wawer M, NK Sewankambo, D Serwadda, et al. 1999. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *The Lancet* 353:525-535.

136 Kamali A, Quigley M, et al. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003;vol 361:645-652

137 Sangani P, Rutherford G, Wilkinson D. Population-based interventions for reducing sexually transmitted infections, including HIV infection. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD001220. DOI: 10.1002/14651858.CD001220.pub2.

138 Freeman EE et al. Proportion of new HIV infections attributable to herpes simplex 2 increases over time: simulations of the changing role sexually transmitted infections in sub-Saharan African HIV epidemics. *Sex Transm Infect* 83 (suppl 1): i17-i24, 2007.

139 Freeman EE et al. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 20(1):73-83, 2006.

recipients<sup>140 141</sup>. Analysis of one of these studies, conducted in Tanzania, led Deborah Watson-Jones and colleagues to conclude:

- Acyclovir has a short half-life and poor absorption; the drug may not fully suppress HSV-2 replication, leading to sub-clinical reactivations of HSV-2 that are sufficient to increase the risk of HIV infection. Valacyclovir or higher doses of acyclovir (800mg bid) may be more potent options for study.
- Adherence was poor: Biological measures of adherence in the study (urine excretion of acyclovir) showed that after 24 months on treatment, only 33% showed evidence of acyclovir, compared to 60% at six months. Median self-reported adherence during the study was 90%<sup>142</sup>.

In contrast, adherence to study drug was excellent among African women and gay men in Peru and the United States in the HPTN 039 study (pill counts indicated that 87% of all doses were taken)<sup>143</sup>. HSV-positive genital ulcers were significantly decreased by 67%, with less response among African women than among MSM and overall, a lower reduction in incidence of genital ulcer disease than expected based on prior studies of acyclovir for HSV-2 suppression. Follow-up studies are underway to evaluate pharmacokinetics of acyclovir and the clinical and virologic response of genital herpes to acyclovir among African women.

A study of the potential of acyclovir to reduce HIV transmission in HIV-discordant partnerships where the HIV-positive partner is coinfectd with HSV-2, is ongoing in sub-Saharan Africa and expected to report in February 2009.

Valacyclovir, a prodrug of acyclovir that promotes greater bioavailability, has been studied in two randomised ANRS studies (ANRS 1285a & b) in HIV-positive women on and off antiretroviral therapy. In women receiving HAART, valacyclovir reduced HSV-2 shedding but had no significant effect on HIV shedding in genital fluids<sup>144</sup>. In women not receiving antiretroviral therapy, valacyclovir therapy was associated with a 0.3 log reduction in genital HIV and a 60% reduction in the frequency of HIV detection in genital fluids during the 12 weeks study<sup>145</sup>.

Two randomised, placebo-controlled crossover studies in Peru showed a reduction in plasma and rectal HIV levels among MSM<sup>146</sup> and in cervical and anogenital HIV levels in women<sup>147</sup> during eight weeks of valacyclovir exposure.

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140 Watson-Jones D et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. *N Engl J Med* 358(15):1560-71, 2008.

141 Celum C et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet* 371(9630):2109-19, 2008.

142 Watson-Jones D et al, *ibid*.

143 Celum, *op cit*.

144 Ouedraogo A, Nagot N, Vergne L, et al. Impact of suppressive herpes therapy on genital HIV-1 RNA among women taking antiretroviral therapy: a randomized controlled trial. *AIDS* 2006 Nov 28;20(18):2305-13

145 Nagot N, Ouedraogo A, Foulongne V, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007 Feb 22;356(8):790-9

146 Zuckerman RA et al. Herpes simplex virus (HSV) suppression with valaciclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomised, double blind, placebo-controlled crossover trial. *J Infect Dis* 196: 1500 – 1508, 2007.

147 Baeten J et al. Herpes simplex virus suppressive treatment decreases plasma and genital HIV-1 viral loads in HSV-2/HIV-1 co-infected women: a randomized, placebo-controlled, cross-over trial. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston.

The disadvantage of both acyclovir and valacyclovir is their short half-lives and the need for twice-daily dosing. Given recent data indicating frequent bursts of subclinical HSV-2 reactivation<sup>148</sup> and persistent genital immune response after HSV-2 reactivations<sup>149</sup>, more potent and/or combination interventions may be needed to suppress the mechanism by which HSV-2 increases HIV susceptibility.

An HSV-2 vaccine is a long-standing subject of research. Although HSV-2 infection is widespread in sexually active adults in sub-Saharan Africa, an effective vaccine might contribute to long-term HIV prevention if it was administered to infants.

An HSV-2 vaccine is currently being tested in the Herpevac phase III study in HIV-negative, HSV-1 and HSV-2 seronegative women in the United States. Preceding studies of this vaccine, *Simplirix*, showed 73% efficacy against the development of genital herpes in HSV-1 & 2 negative women. The vaccine did not show efficacy in women who were HSV-2 negative but already infected with HSV-1, nor did it have a protective effect in men<sup>150</sup>. In another trial, a therapeutic vaccine candidate failed to reduce the recurrence of genital herpes or asymptomatic shedding in men and women<sup>151</sup>.

### 3.11.2 Future research questions

Regarding HSV-2 suppressive therapy:

- Is higher dose acyclovir more effective than standard dosing at protecting against HIV infection, or at reducing HIV transmission from HIV-positive to HIV-uninfected partners?
- Would valacyclovir have a greater efficacy than acyclovir?
- Can long-term suppressive therapy reduce the degree of immune activation associated with HSV-2 infection?

There are several unanswered questions in HSV-2 vaccine development as it relates to HIV prevention:

- Since HSV-2 vaccine development is not focused on sterilising immunity, how much will an HSV-2 suppressive vaccine contribute to reducing immune activation in the genital tract or HIV shedding in those already infected with HIV?
- How much investigation of sub-clinical lesion frequency and HSV-2 DNA shedding would be necessary before it was worthwhile putting an HSV-2 vaccine into HIV prevention trials? Which assays would need to be standardised before such trials could take place?
- Would a gender-specific HSV-2 vaccine be of value in HIV prevention? If the

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Abstract 676. 2008.

148 Mark KE et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis* 198(8):1141-9, 2008.

149 Zhu J et al. Virus-specific CD8+ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. *J Exp Med* 204(3):595-603, 2007.

150 Spruance S Gender-specific Efficacy of a Prophylactic SBAS4-Adjuvanted gD2 Subunit Vaccine Against Genital Herpes Disease (GHD): Results of Two Clinical Efficacy Trials. *Abstr Intersci Conf Antimicrob Agents Chemother Intersci Conf Antimicrob Agents Chemother*. 2000 Sep 17-20; 40: 180

151 De Bruyn G et al. A randomized controlled trial of a replication defective (gH deletion) herpes simplex virus vaccine for the treatment of recurrent genital herpes among immunocompetent subjects. *Vaccine* 2006 Feb 13;24(7):914-20.

current vaccine was shown to be effective in seronegative women, would its durability of protection be effective if given in early childhood?

- What could a therapeutic HSV-2 vaccine contribute to HIV prevention goals?

### **3.12 Vaccines**

The promise of an effective HIV vaccine has always been just over the horizon, but more than 20 years after the identification of HIV, vaccines remain far from implementation. Today we recognise that the development of an HIV vaccine is one of the most difficult challenges confronting biomedical research.

Broadly speaking, vaccine research has taken two paths: induction of neutralising antibodies, and/or of cell-mediated immunity. The ultimate aim is a vaccine that induces both arms of the immune response.

Trials of vaccines designed to induce neutralising antibodies have produced disappointing results to date. Two VaxGen subunit vaccines (named AIDSVAX), one composed of subtype B sequences, the other of subtypes E and B, have been tested in large efficacy studies in the Americas/Netherlands and Thailand<sup>152</sup> respectively, and shown no protective effect.

Vaccines that induce solely cell-mediated immune responses have been regarded as an interim but perhaps more immediately pursuable avenue of research because T-cell responses can be directed to conserved regions of the virus and hence protect against a wider variety of infecting strains, despite an incomplete understanding of the immunological correlates of protection against HIV infection. So-called T-cell vaccines have been mainly conceptualised as a means of slowing HIV disease progression in vaccine recipients who subsequently become infected, and possibly also decreasing secondary transmission of the virus to the sexual partners of vaccinated individuals.

In September 2007 the STEP trial of Merck's adenovirus 5-vectored vaccine containing sequences of HIV's *gag*, *pol* and *nef* genes was halted by the DSMB based on a futility analysis. Subsequent analysis revealed a trend towards a higher rate of infection in those who received the vaccine than in the placebo group. Additional post hoc analysis of male volunteers showed the highest relative risk of infection in vaccine recipients compared to placebo recipients was in uncircumcised men with pre-existing neutralising antibodies to adenovirus at the time of enrollment<sup>153 154</sup>.

The termination of the Merck Ad5-vectored vaccine study has been viewed as a huge setback for the T-cell vaccine approach. A phase IIb study of a somewhat similar approach developed by the NIH's Vaccine Research Center (VRC), but using a prime-boost dosing schedule with a multi-clade DNA prime and a different Ad5-vector boost – a strategy that includes envelope as well as *gag*, *nef* and *pol* sequences – is still under consideration. The

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152 Pittsittithum P et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. *J Infect Dis* 194(12):1661-71, 2006.

153 Robertson M, Buchbinder S et al. Efficacy results from the STEP Study (Merck V520 protocol 023/HVTN 502): a phase II test-of-concept trial of the MRKad5 HIV-1 *gag/pol/nef* trivalent vaccine. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 88LB, 2008.

154 Robertson M et al. Immunological characterization of subjects from the STEP Study: a phase IIB test-of-concept trial of the MRKad5 HIV-1 *gag/pol/nef* trivalent vaccine. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 89LB, 2008.

trial of the VRC vaccine regimen has been widely debated and a new protocol for a small, focused test-of-concept trial is being developed and could begin in 2009. Advocates for testing the VRC vaccines have argued that the study will be important to improve understanding of the strengths and limitations of vaccines designed to stimulate cell-mediated immunity against HIV.

Other potential T-cell vaccine candidates include several modified vaccinia Ankara (MVA) vectors, other poxvirus vectors, other viral vectors, as well as DNA vaccines administered with or without viral vectors, adjuvants and/or electroporation.

A phase III study of ALVAC vcp1521 (a CTL-inducing vaccine) and AIDSVAX B/E as a prime/boost regimen is currently underway in over 16, 000 volunteers in Thailand, with results expected late in 2009. The study underwent a DSMB interim efficacy analysis in June 2007 as well as subsequent analysis for futility, and continues. Phase II studies of ALVAC suggested it induced CTL responses in less than 30% of individuals<sup>155</sup>.

Details of other human trials in phase I and II can be found in Appendix 2.

The STEP trial did help to advance the field by (a) verifying that a phase IIb trial design can answer questions about vaccine efficacy and safety in an rapid, efficient and effective manner; (b) demonstrating that some non-human primate models may be less reflective of human outcomes than other models; and (c) pointing to the need for better laboratory immune monitoring tools that might better reflect the in vivo activity of a vaccine candidate.

### **3.12.1 Future research questions**

The setback of the STEP trial results has catalysed agreement within the field that more investment is needed in discovery research.

A recent HIV vaccine summit held by the US National Institutes of Health in March 2008 heard widespread calls from the field for further investment in discovery research as opposed to product development. Importantly, participants recognised that laboratory, animal model and clinical research were all needed to help inform vaccine discovery. The NIH has taken subsequent action to shift the balance of their investment more toward discovery research<sup>156</sup>.

Areas of greatest focus identified in the scientific plan of the Global HIV Vaccine Enterprise (see below) include:

- Neutralising antibodies; which antibodies are protective against HIV infection in vivo; which epitopes induce those antibodies; how is the B-cell response disrupted by HIV infection; how might the B-cell response be improved? Which sites of antibody activity have most relevance for protection against HIV?
- How can be vaccines be designed that elicit both cell-mediated and neutralising antibody responses?
- Animal model research: how can models be improved, and how can the data inform product studies rapidly?

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155 Thongcharoen P et al. A phase 1/2 comparative vaccine trial of the safety and immunogenicity of a CRF01\_AE (subtype E) candidate vaccine: ALVAC-HIV (vCP1521) prime with oligomeric gp160 (92TH023/LAI-DID) or bivalent gp120 (CM235/SF2) boost. *J Acquir Immune Defic Syndr* 46(1):48-55, 2007.

156 Fauci AS, Johnston MI, Dieffenbach CW, et al. HIV vaccine research: the way forward. *Science* 2008;321:530-2



- Vectors: which viruses are most suitable as vectors for use in vaccine development? Might other vectors be more suitable than adenoviruses?
- Live attenuated vaccines: can a safe and effective live attenuated vaccine be developed?
- Mucosal and innate immunity: what are the earliest events in HIV infection, occurring at the mucosal surface? What assays are needed to measure mucosal cellular responses? What are the earliest innate immune responses to HIV infection? Can innate intracellular factors such as APOBEC3G and other innate components such as natural killer cells be harnessed to control HIV through a vaccine approach?<sup>157</sup>
- Correlates of protection: what is an effective T-cell response and what assays need to be developed to measure that response? What investments are needed to improve assays for measurement of cellular and humoral responses?
- Laboratory standardisation: develop new assays, standardise between laboratories, develop a network of reference laboratories and develop a global quality assurance programme.
- Product development and manufacturing: how can limited global expertise in developing consistent, active batches of vaccine at large scale be leveraged to support the global research effort and ensure that manufacturing capacity is available as vaccines come closer to licensing?
- Clinical trials capacity: how can the capacity to run multiple large clinical trials of vaccine candidates simultaneously be enhanced globally?
- Regulatory issues: how can global regulatory capacity for vaccine approval be increased? How can differing regulatory needs of developing countries and developed world be addressed?
- Intellectual property: how should intellectual property agreements be structured in order to ensure greatest access and sharing of information while encouraging innovation?

Research priorities have been reviewed in more detail by the Global HIV Vaccine Enterprise<sup>158</sup>, NIAID<sup>159</sup>, the AIDS Vaccine Advocacy Coalition<sup>160</sup> and IAVI<sup>161</sup>.

### **3.12.2 Current investments in vaccine development**

HIV vaccine research is the first area of HIV research in which donors and scientists have developed a comprehensive international research framework.

Recognising the challenge of developing an HIV vaccine, in 2003 a group of HIV scientists proposed the creation of the Global HIV Vaccine Enterprise. The Enterprise is an alliance of independent organizations around the world that promotes innovation and collaboration

<sup>157</sup> Shattock RJ et al. Improving defences at the portal of HIV entry: mucosal and innate immunity. PLoS Medicine 5(4): e81, 2008.

<sup>158</sup> Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise. The Global HIV/AIDS Vaccine Enterprise: scientific strategic plan. PLoS Medicine 2 (2): e25, 2005.

<sup>159</sup> Fauci AS, Johnston MI, Dieffenbach CW, et al. HIV vaccine research: the way forward. Science 2008;321:530-2.

<sup>160</sup> AVAC. Resetting the clock: annual report 2007. <http://www.avac.org/reports.htm>

<sup>161</sup> International AIDS Vaccine Initiative. Learning from the past, building from the future: IAVI strategic plan 2008-2012.

to speed the search for an HIV vaccine ([www.hivvaccineenterprise.org](http://www.hivvaccineenterprise.org)).

The first Scientific Strategic Plan of the Enterprise was published in 2005<sup>162</sup> identifying priority research in six areas: Vaccine Discovery, Laboratory Standardization, Product Development and Manufacturing, Clinical Trials Capacity, Regulatory Aspects and Intellectual Property Issues. More recently the Enterprise made additional recommendations in the areas of antibody-based vaccines<sup>163</sup> (PLoS Medicine December 2007) and mucosal and innate immunity<sup>164</sup> (PLoS Medicine, April 2008).

The following areas are already focuses for research supported by NIH, IAVI, the Bill & Melinda Gates Foundation and others, coordinated within the Global Vaccine Enterprise:

- NIH supports research to identify and better understand protective immune responses to HIV, and information gleaned from these studies is being used to inform the design and development of novel vaccine strategies. NIH vaccine research include several goals:
  - Increase scientific knowledge through basic and animal model research.
  - Design and evaluate HIV antigens, adjuvants and vaccine delivery methods.
  - Conduct clinical research to assess the safety, immunogenicity and efficacy of suitable candidate vaccines and to explore fundamental questions to guide vaccine discovery.
  - Develop strategies, infrastructures and collaborations with different partners.
- In response to the Enterprise plan, in 2005 NIH established the Center for HIV/AIDS Vaccine Immunology (CHAVI), a consortium of more than 100 scientists in more than 38 institutions, including 13 clinical sites, who are trying to solve major problems in HIV vaccine research through the work of 10 highly collaborative Discovery Teams supported by 10 cores.
- IAVI supports the design, development, and clinical evaluation of HIV vaccine candidates applicable for use in developing countries through a range of partnerships and agreements with more than 40 academic, biotechnology, pharmaceutical, and government institutions around the world. Some of its activities are:
  - Neutralising Antibody Consortium: identification of consistently conserved epitopes across sub-types with powerful neutralising effects could lead to a new generation of antibody-based vaccines.
  - Live Attenuated Vaccines Consortium: dedicated to understanding the protective characteristics of live attenuated vaccines in animal models.
  - Vectors Consortium: investigating novel vectors for delivery.
- The Bill & Melinda Gates Foundation has aligned its strategy with the Enterprise Plan and is supporting a number of activities:
  - One of the main activities is the Collaboration for AIDS Vaccine Discovery (CAVD), established in 2006 as a large network of 18 research consortia that

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162 Coordinating Committee of the Global Vaccine Enterprise. The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan. PLoS Medicine 2 (2), e25: 0111-0121, 2005.

163 Montefiori D et al. Antibody-based HIV-1 vaccines: recent developments and future directions. PLoS Medicine 4(12):e348, 2007.

164 Shattock R, *ibid*.

involve more than 100 investigators in over 100 institutions in more than 20 countries. Thirteen of the groups are Vaccine Discovery Consortia exploring different approaches to development of vaccines aimed at inducing humoral or cell-mediated immune responses. Five CAVD consortia are Central Service facilities that provide standardised evaluation of immune responses, data analysis and statistical support and repository facilities. The CAVD is held together by an Alliance Management system and by an agreed-upon data and material sharing agreement.

- The Canadian HIV Vaccine Initiative is a collaboration between the Government of Canada and the Bill & Melinda Gates Foundation.
  - Discovery and social research into vaccine acceptability.
  - Clinical trial capacity building in low and middle income countries.
  - Pilot scale manufacturing facility in Canada for clinical trial lots to serve as a global resource for vaccine efforts.
  - Policy and regulatory issues/community and social dimensions: policy analysis of the legal, ethical and human rights dimensions of HIV vaccine development, clinical trials, delivery and access; community engagement.
- The French National Agency for AIDS Research's priorities include:
  - Identification of innate immune mechanisms, with a particular focus on dendritic cell/natural killer cell interactions.
  - Development of vaccine candidates targeting HIV antigens to dendritic cells.
  - Assessment of immunogens in animal models.
  - Phase I and II clinical trials of prophylactic and therapeutic vaccines.
- Europrise is a European Union research and development platform that combines vaccine and microbicide research within one framework. Priorities include:
  - Standardisation and harmonisation of research tools.
  - Identification of new HIV/AIDS vaccine and microbicide candidates and combinations to prevent HIV/AIDS.
  - Establishment of clinical development pathway for vaccines and microbicides within a European framework.
  - Provision of scientific training in microbicide and vaccine development.
  - To facilitate access to information relevant to HIV microbicides and vaccines.
  - Provision of a single focus for European HIV microbicide and vaccine research.
- African AIDS Vaccine Programme priorities include:
  - Building research and regulatory capacity in Africa.
  - Increasing capacity for ethical review.
  - Supporting country-based strategic planning on National HIV Vaccine Plans.
  - Promote advocacy, policy development, community involvement and networking around vaccines in Africa.

Of note, investment in vaccine research comes overwhelmingly from the public sector and foundations; only one company (Merck) has invested more than \$10 million annually in vaccine research. Companies cite the current scientific uncertainty and the lack of incentives for conducting phase II studies and investigating process development as barriers to entry to the field<sup>165</sup>.

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<sup>165</sup> AVAC, *ibid*, p22.

## 4 Antiretroviral treatment

This document refers to and builds on the *2008 Pipeline Report* by the Treatment Action Group (TAG), published in July 2008<sup>166</sup>. That report identified key experimental treatments and preventive therapies for HIV, hepatitis C, and tuberculosis, with an emphasis on products that had already reached at least Phase II clinical trials.

As new antiretroviral therapeutics continue to emerge, it is clear that we are at a watershed for antiretroviral care. As the 2007 edition of the TAG report stated, "not since the *annus mirabilis* of HIV therapy in 1996 have so many potent new drugs neared the market [all] at almost the same time."<sup>167</sup> Moreover, after a time when most new agents offered incremental or debatable advantages over existing drugs, many of the currently emerging agents offer significant strategic advantages, particularly for highly treatment-experienced patients.

Many are the first of entirely new antiretroviral classes, whose distinct new mechanisms of action virtually guarantee effectiveness even against highly drug-resistant forms of the virus. Many new additions to existing drug classes exhibit distinctive resistance profiles, and the fact that many are reaching the market simultaneously allows for the construction of highly effective new combinations.

Recent research has also demonstrated that currently available drugs are capable of total suppression of ongoing viral replication in previously untreated individuals (see *Pathogenesis research* below), while analyses of viral suppression and mortality rates in cohorts of HIV-positive people on treatment have led to projections of a near-normal life expectancy for those who begin treatment today in their 20s and 30s<sup>168 169</sup>.

This transformation in the long-term prognosis of people with HIV in the developed world has been tempered by the finding of an elevated risk of non-AIDS defining cancers in people with HIV<sup>170</sup>, along with evidence of an elevated risk of cardiovascular disease in patients receiving protease inhibitor-based HAART or regimens containing abacavir or didanosine<sup>171 172</sup>.

The challenge for the next two decades is to extend these improvements in care and prognosis to people with HIV in low- and middle-income settings, and to achieve sustainable universal access to antiretroviral therapy.

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166 Treatment Action Group. The 2008 Pipeline Report: Experimental treatments and preventive therapies for HIV, hepatitis C, and tuberculosis. July 2008.

167 Treatment Action Group. The 2007 Pipeline Report: Experimental treatments and preventive therapies for HIV, hepatitis C, and tuberculosis. July 2007.

168 The Antiretroviral Cohort Collaboration. Life expectancy of individuals on combination therapy in high-income countries: a collaborative analysis of 14 cohort studies. *The Lancet* 372: 293 – 299, 2008.

169 Lohse N et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. *Annals of Internal Medicine*:146: 87-95, 2007.

170 Patel P et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Annals of Internal Medicine* 148 (10): 728-736, 2008.

171 The DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 356: 1723-1735, 2007.

172 The DAD Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *The Lancet* 371(9622):1417-26, 2008.

## 4.1 Existing drug classes

Currently, six major classes of antiretroviral drugs are approved for use:

- **Fusion inhibitors**, which prevent HIV from entering target cells by binding to the viral envelope protein, gp41.
- **CCR5 inhibitors**, which also prevent HIV cellular entry, in this case by blocking the CCR5 co-receptor also required for viral entry.
- **Nucleoside analogue reverse transcriptase inhibitors (NRTIs)**, which inhibit the synthesis of proviral DNA by reverse transcriptase. Nucleoside analogues act as false viral nucleosides, terminating the construction of the proviral DNA chain to which they are added.
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**, which also inhibit the synthesis of viral DNA, in this case by binding to the reverse transcriptase enzyme. (NRTIs and NNRTIs are subclasses of the larger class of **reverse transcriptase inhibitors** – see figure below.)
- **Integrase inhibitors**, which prevent proviral DNA from being incorporated into the host cell DNA.
- **Protease inhibitors**, which bind to the active site of the viral protease enzyme, preventing the processing of viral proteins into functional forms.

Approved, established products in clinical use comprise the following<sup>173</sup>:

Drug class	Non-proprietary names	Brand names	Manufacturer
<b>Fusion inhibitors</b>	enfuvirtide, T-20	<i>Fuzeon</i>	Roche
<b>CCR5 inhibitors</b>	Maraviroc	<i>Celsentri/Selzentry</i>	Pfizer
<b>Nucleoside analogues</b>	Abacavir didanosine, ddl Emtricitabine Lamivudine stavudine, d4T tenofovir* zidovudine, AZT	<i>Ziagen</i> <i>Videx, Videx EC</i> <i>Emtriva</i> <i>3TC, Epivir</i> <i>Zerit</i> <i>Viread</i> <i>Retrovir</i>	GlaxoSmithKline (GSK) Bristol-Myers Squibb (BMS) Gilead GSK BMS Gilead GSK
<b>NNRTIs</b>	delavirdine efavirenz nevirapine etravirine	<i>Rescriptor</i> <i>Sustiva, Stocrin</i> <i>Viramune</i> <i>Intence</i>	Pfizer BMS/Merck Boehringer-Ingelheim (BI) Tibotec
<b>Integrase inhibitors</b>	raltegravir	<i>Isentress</i>	Merck

<sup>173</sup> Current as of October 2008.

Drug class	Non-proprietary names	Brand names	Manufacturer
<b>Protease inhibitors</b>			
	atazanavir	<i>Reyataz</i>	BMS
	darunavir	<i>Prezista</i>	Tibotec
	fosamprenavir	<i>Lexiva</i>	GSK
	indinavir	<i>Crixivan</i>	Merck
	lopinavir/ritonavir	<i>Kaletra</i>	Abbott
	nelfinavir	<i>Viracept</i>	Pfizer/Roche
	ritonavir	<i>Norvir</i>	Abbott
	saquinavir	<i>Invirase</i>	Roche
	tipranavir	<i>Aptivus</i>	BI

(\* tenofovir is technically a **nucleotide analogue**, a molecule structurally distinguished from nucleoside analogues only by an additional phosphoryl group.)

#### 4.1.1 Developmental products in existing/emerging classes

What is particularly notable about the pipeline of new antiretrovirals is the extent to which development is concentrated among smaller biotechnology companies, and that after a period of rapid expansion in new antiretroviral classes, only one new class with wide potential for use – maturation inhibitors – is currently in development.

Drug class	Non-proprietary names	Phase	Manufacturer	Potential advantages	Disadvantages
<b>CCR5 antagonists</b>					
	Vicriviroc INCB9471	3 2a/b	Schering Plough Incyte	Once daily, long half-life	Ritonavir-boosting* Stalled in development, looking to out-license due to cost
	PRO 140 (monoclonal antibody)	2a	Progenics	Dosed once every 2-3 weeks  No cross-resistance with other CCR5 antagonists	Currently intravenous although subcutaneous product planned
	SCH532706 HGS004 (monoclonal antibody)	1b 1	Schering Plough Human Genome Sciences	Once daily	Ritonavir-boosting Currently intravenous
<b>Nucleoside analogues</b>					
	Apricitabine	3	Avexa	Activity against 3TC-resistant virus	Twice-daily
	Elvucitabine	2b	Achillion	Very long half-life, once-weekly dosing potential	
	dexelvucitabine	2a	Pharmasset	Once daily, Activity against TAMs	Potential pancreatic toxicity Looking for new development partner
	Racivir	2	Pharmasset		Not active against extensively NRTI resistant virus

Drug class	Non-proprietary names	Phase	Manufacturer	Potential advantages	Disadvantages
<b>NNRTIs</b>	Rilpivirine	3	Tibotec	Once daily	
				Active against viruses resistant to first line NNRTIs	
				Low potential for drug interactions	
	UK-453,061	2b	Pfizer	Potentially cheap to produce As above – also once daily potential	
	RDEA806	2a	Ardea Biosciences		
<b>Protease inhibitors</b>					
	MK-8122	1	Merck	No ritonavir-boosting	
<b>Integrase inhibitors</b>					
	Elvitegravir	2b	Gilead		Ritonavir-boosted
<b>Maturation inhibitor</b>					
	Bevirimat	2b	Panacos		Gag mutation testing required, may be unsuitable for up to 50% of treatment-experienced
<b>Antisense gene therapy</b>					
	VRX496	1/2	VIRxSYS		Requires autologous T-cell administration by infusion

\*Ritonavir is used at a low dose to boost plasma levels of all currently prescribed protease inhibitors, but has a number of disadvantages including problematic drug interactions with a wide range of medicines, an association with elevated triglycerides, and high cost. Any replacement product would share the problematic drug interactions of ritonavir. Ritonavir-boosting is not disadvantageous if the background regimen already contains another ritonavir-boosted drug, since one dose of ritonavir will have a similar boosting effect on all drugs in the regimen that are metabolised through the same pathway.

For developing countries the highest priority for drug development is low cost products that can be used in second-line treatment. High-level resistance to many elements of first-line treatment emerges frequently due to lack of viral load testing and delayed switching to second-line treatment. The most common forms of resistance are high-level resistance to 3TC and FTC, and high-level cross-resistance between currently available drugs of the NNRTI class. Although less common, a substantial minority of patients also develop high-level nucleoside analogue resistance upon failure of first-line treatment<sup>174 175</sup>. Drug development will need to keep pace with the emerging patterns of resistance in populations in low-income countries.

174 Boyd MA, Copper DA. Second-line combination antiretroviral therapy in resource-limited settings: facing the challenges through clinical research. AIDS. 21 Suppl 4:S55-S63, July 2007

175 Bennett DE et al. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. Antiviral Therapy 13 (supp 2): 1-13, 2008.



Particular long-term needs for developing world treatment include:

- A second-line low-cost nucleoside analogue that is active against 3TC and FTC-resistant virus **and** which can be coformulated with tenofovir, particularly for use in developing countries.
- A second-line low-cost nucleoside analogue that is active against virus with high-level thymidine analogue resistance, particularly for use in developing countries (abacavir, a WHO-recommended second-line agent, has reduced activity against high level thymidine analogue resistant virus).
- A low cost integrase inhibitor that can be used in second line treatment in developing countries.
- At least one new drug class that is cheap to produce, well tolerated, free from long-term adverse effects and which requires no diagnostic test before use.

This list of priorities is driven primarily by the development of resistance rather than the need to reduce the cost of treatment and is unlikely to change with the expiration of patents on many of the current antiretroviral agents.

However, these needs may not be paramount in Europe and North America, particularly if there continues to be greater access to a wider variety of drugs and drug classes due to price and patent restrictions. In these circumstances, how should drug discovery efforts that respond primarily to the needs of the developing world be financed and encouraged?

In addition there is concern that innovation in new and existing classes for treatment-naïve patients in Europe and North America may be stifled by the current regulatory assumption that no unmet need exists for this group of patients<sup>176</sup>.

## 4.2 Longer-term class developments

A number of viral and cellular targets are under investigation, but remain largely in the basic science research stage. These include:

- **Silencing RNAs** – nucleotide sequences which mirror very short sequences of messenger RNA – promising in vitro results but will one siRNA be effective against all viral subtypes and mutants? Will foreign RNAs stimulate immune activation? How will the very short half-life of SiRNAs be dealt with? What is the potential for cross-reaction with other gene sequences, leading to toxicity?
- **Antisense oligonucleotides** are nucleotides designed to bind to sequences of messenger RNA in order to prevent the production of the protein encoded by that mRNA. These may have similar drawbacks to siRNAs.

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<sup>176</sup> See presentations by Jeff Murray and Nathalie Morgensztejn, Forum for Collaborative HIV Research meeting 'Re-thinking the Design of Clinical Trials for the Development of New ARVS for Treatment Experienced and Treatment Naïve Patient Populations', <http://www.hivforum.org/projects/Clinical%20Trial%20Design.htm>

- **Inhibitors of HIV's *tat* enzyme:** Rs22 ribozyme (Johnson & Johnson).
- **Inhibitors of HIV's *vpr* enzyme:** mifepristone (RU-486) is being tested by VGX Pharmaceuticals.

### Host cell proteins as new drug targets

Numerous host cell proteins with antiretroviral action are also the subjects of basic science research<sup>177</sup>. One such protein, **TRIM5**, recognises retroviral capsid proteins in infected cells and inactivates the retrovirus by an as yet unknown process. Another, **APOBEC3**, infiltrates newly produced viruses and degrades their genetic material.

Genomic screening is also revealing a growing number of host cell proteins that interact with HIV during its life cycle<sup>178</sup>. The challenge will be to identify the most appropriate therapeutic targets. To be a suitable therapeutic target a host cell protein must be indispensable to viral replication, but must have a dispensable function in the host.

## 4.3 Formulation developments

Improving the ease of taking treatment is likely to improve adherence. Developments in formulations may also make therapy more potent, by allowing drugs to reach currently inaccessible reservoirs of HIV within the body. Formulation improvements also have the potential to expand access and lower the cost of treatment in the developing world.

### 4.3.1 Fixed-dose co-formulations

**Fixed-dose combinations (FDCs)**, or co-formulations, offer considerable advantages over regimens of individually-formulated drugs. The dosing simplicity and reduced pill burden of FDCs has made them especially attractive for use in developing countries. FDC development has been led by generic manufacturers in India who have taken advantage of lack of local patenting on older antiretroviral products to combine products from multiple originators in single pills. FDC development has continued in India with voluntary licensing of newer antiretroviral drugs.

There are clinical and pharmacological issues unique to FDCs, which may preclude or present challenges to the packaging of drugs into a single capsule. These include:

- Different dosing schedules of constituent drugs.
- Variable dosing and pharmacokinetics, such as in paediatrics or the dose escalation recommended for nevirapine.
- Chemical incompatibilities between constituent drugs.

<sup>177</sup> Bieniasz P. New insights into retrovirus-host-cell interactions. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 114, 2008.

<sup>178</sup> Brass ML et al. Identification of host proteins required for HIV infection through a functional genomic screen. *Science* 319(5865):921-6, 2008.

Cross-pharmaceutical collaboration is also required when different components are manufactured by different companies – a situation specific to FDCs. Only two originator companies have successfully collaborated to date on a fixed dose combination of their products; Gilead and Bristol Myers-Squibb combined tenofovir, emtricitabine and efavirenz in one pill, launched as *Atripla* in 2007 in the United States.

#### **4.3.2 Fixed-dose combinations: Paediatric formulations**

Paediatric FDC formulations are a particular challenge due to the need to tailor drug dosages to constantly changing body weight and metabolism. Paediatric dosing is also complicated by the fact that the rate at which drugs are processed in children changes as they grow, and it is not safe to infer paediatric doses from adult dosing recommendations.

PEPFAR convened a public-private partnership between originator and generic manufacturers and multilateral agencies in 2006 to develop fixed-dose paediatric combinations; so far no cross-company collaborations by originators have resulted in product licensing. However several Indian generic companies have developed paediatric fixed dose combinations. Cipla has developed a paediatric version of stavudine/lamivudine/nevirapine (*Triomune*) that is now licensed for PEPFAR use. Ranbaxy continues development of a d4T/3TC/nevirapine tablet for children. All of these tablets are scored to provide dosing flexibility, Paediatric fixed dose combination tablets are also crushable and dispersible for ease of dosing.

In 2006 a WHO expert panel highlighted the need for fixed dose combinations for children as urgent, requesting AZT/3TC and d4T/3TC tablets, together with the need for international agreement on the ratios of drugs that need to be included in fixed-dose combinations for children<sup>179</sup>.

The WHO recently released a harmonised and simplified dosing schedule that permits providers equipped with a small range of FDC products to dose all children above 6 weeks with the same weight-band based tablet schedule irrespective of the regimen<sup>180</sup>.

This type of innovative approach is crucial to ensure that paediatric treatment is decentralised in the health system. Paediatric FDCs represent a significant advance that simplify treatment for providers and make it easier for children to remain adherent to treatment.

Emerging needs include heat stable ritonavir-boosted protease inhibitor formulations for infants, in the form of powder that can be sprinkled on food, and a paediatric version of tenofovir.

There is also a persisting challenge regarding the palatability of paediatric formulations, and more work needs to be done to find ways of delivering medicines to children that cannot take tablets, in ways that will ensure good adherence to the medicines.

#### **4.3.3 Extended-release products**

Extended-release formulations may allow for less frequent dosing of antiretrovirals such as

<sup>179</sup> Summary statement on WHO recommendations on ARV medicines for treating and preventing HIV infections in younger children.

November 2006. <http://www.who.int/hiv/mediacentre/news63/en/index.html>

<sup>180</sup> [http://www.who.int/hiv/paediatric/Sum\\_WHO\\_ARV\\_Ped\\_ARV\\_dosing.pdf](http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf)

nevirapine, whose pharmacokinetics would otherwise preclude it. An extended-release formulation of stavudine (d4T), suitable for daily dosing, was developed some years ago<sup>181</sup>, and Boehringer-Ingelheim has recently announced an international trial of an extended-release, once-daily formulation of nevirapine<sup>182</sup>. The VEXVE trial is a double-blind study comparing nevirapine 400 mg extended-release formulation, given as one pill once a day, to the currently approved nevirapine regimen, given as one 200 mg tablet twice daily.

#### 4.3.4 Dose reduction

There is evidence of potential to reduce the doses of several important drugs used in HIV treatment without loss of efficacy, also leading to reduced toxicity. Randomised studies are currently being designed to test lower doses of efavirenz, ritonavir-boosted lopinavir, zidovudine and lamivudine (3TC).

According to calculations by the Clinton HIV/AIDS Initiative, dose reduction alone could reduce the annual per-patient price of the first-line regimen of AZT+3TC+EFV from \$293 today to less than \$180. Similarly, second-line therapy with TDF+3TC+LPV/r could drop from today's price of \$679 to approximately \$400. Looking ahead five years, a successful 'naked' dose reduction programme could produce aggregate savings of more than \$150 million per year and thereby make universal access to antiretroviral therapy a much more sustainable proposition. Further, ARV manufacturing capacity needs could decrease by over 25%.

Reformulation of drugs to increase their bioavailability could also permit dose reduction and cost savings. For example, a reformulation of tenofovir disoproxil (the pro-drug of tenofovir) to tenofovir and an extension of the drug's half-life could potentially reduce its cost by up to 80%.<sup>183</sup>

#### 4.3.5 Nanotechnology and therapeutics (improved delivery methods)

Drug delivery systems using nanotechnology are already being used in cancer treatment to target drugs more closely to their actual sites of action, increasing drug efficacy while decreasing systemic toxicities. Nanotechnology-based drug delivery systems for antiretrovirals are now in the initial stages of development<sup>184</sup>. The goals of such delivery systems are to facilitate antiretroviral delivery, both at an intracellular level and to anatomical reservoirs where drug penetration is currently limited (notably, the central nervous system, where the blood-brain barrier impedes drug penetration).

Many nanodelivery systems are based on encapsulating or otherwise binding active drug molecules (the "therapeutic payload") with biodegradable polymers and lipids engineered to maximise delivery to the intended target. For example, intracellular delivery can be facilitated by nanocarriers containing molecules chosen to bind to surface proteins of the target cells. Preliminary, *in vitro* and *in vivo* studies have shown more than tenfold gains in intracellular concentrations of saquinavir and AZT when administered with such nanoengineered delivery

181 Kaul S et al. Pharmacokinetics (PK) of Stavudine (d4T) Extended Release Formulation Compared with Stavudine Immediate Release (IR) Formulation as Part of Potent Antiretroviral Combination Therapy. 9th Conf Retrovir Oppor Infect, Seattle, abstract 430-W, 2002.

182 aidsmap. Boehringer-Ingelheim begins trial of once-daily extended release nevirapine. Feb 13, 2008.

<http://www.aidsmap.com/en/news/D5388537-9059-489F-ABB0-CFEEFF393F82.asp>

183 Clinton HIV/AIDS Initiative. Applying dose reduction methods to control long-term HIV/AIDS treatment costs in developing countries (unpublished, 2008).

184 Shahiwal A & Amiji MM. Nanotechnology-based delivery systems in HIV/AIDS therapy. *Future HIV Ther.* 1(1):49-59, 2007.

systems.

Tibotec has been working to develop a nanoparticle delivery system for its NNRTI rilpivirine; preliminary studies indicate a single intramuscular injection maintains adequate plasma levels for a month, and the formulation is being pursued for therapeutic and prophylactic indications<sup>185</sup>. A proof of concept *in vitro* study has shown that nanoparticle delivery is also possible for efavirenz, ritonavir and lopinavir<sup>186</sup>.

Experimental nanosystems are also being developed to increase drug delivery past the blood-brain barrier to the central nervous system – a significant challenge for current formulations of many drugs.

Nanotechnology is also being used to develop a novel class of candidate drugs, nanoviricides. These experimental therapeutics are “designed to specifically attack enveloped virus particles and to dismantle them.”<sup>187</sup> Preliminary animal studies of HivCide-I™, a proposed HIV therapeutic agent from NanoViricides, Inc. Company’s proposed HIV therapeutic, are beginning in 2008 with results expected within several months.<sup>188</sup>

#### **4.4 Immunotherapy**

Immunotherapy (also known as immunomodulator or immune-based therapy) is directed at the host immune system rather than at the virus. Its goal is to strengthen the host immune response to HIV infection, thus controlling or limiting the effects of the infection.

##### **4.4.1 Interleukin-2**

The most extensively studied immune-based therapy, the cytokine **interleukin-2 (IL-2)**, has been in trials for many years without producing any definitive conclusions about its clinical utility. A large randomised study is currently evaluating the effects of IL-2 in antiretroviral-naïve individuals with CD4 counts above 300 cells/mm<sup>3</sup>. While IL-2 has resulted in dramatic CD4 cell increases in some patients, the smallest gains are seen in those who have the lowest nadir CD4 cell counts<sup>189</sup>. There has also been no clear demonstration that these CD4 cell gains translate to improved long-term clinical benefit.

There has been speculation that IL-2 could be used to delay the need for onset of antiretroviral therapy by boosting CD4 counts in treatment-naïve patients. However, it is unclear whether the clinical prognoses of IL-2-treated patients would be equivalent to those with naturally higher CD4 cell counts. IL-2’s expense, difficulty of administration (it must be given by injection) and significant flu-like, inflammatory side effects also work against it.

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185 Van t’Klooster G et al. Long-acting TMC278, a parenteral-depot formulation delivering therapeutic NNRTI concentrations in preclinical and clinical settings. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston. Abstract 134. 2008.

186 Destache C et al. Ritonavir-, lopinavir-, and efavirenz-containing nanoparticles: in vitro release of ART. Fifteenth conference on Retroviruses and Opportunistic Infections, Boston. Abstract 743. 2008.

187 Nanoviricides Incorporated. <http://www.nanoviricides.com/>

188 European AIDS Treatment Group. NanoViricides to begin animal trials. March 27, 2008. <http://www.eatg.org/news/newsitem.php?id=14609>

189 Markowitz N et al. Nadir CD4+ T Cell Count Predicts Response to Subcutaneous Recombinant Interleukin-2. Clin Infect Dis 37, electronically published 24 September, 2003.

These trade-offs and uncertainties make it highly questionable whether IL-2 will be used to delay the onset of antiretroviral therapy.

#### 4.4.2 Other immune-based therapies

More recently, the cytokine **interleukin-7 (IL-7)** has been investigated as an immune-based therapy. Low IL-7 levels have been linked to the poor CD4 response to HIV therapy seen in many people co infected with hepatitis C virus (HCV)<sup>190</sup>. A recombinant version of IL-7 has been shown to substantially increase CD4 and CD8 cells in phase I/II studies, although transient HIV viral load increases also occurred in some patients<sup>191</sup>. IL-7 will likely continue to be studied as a potential immune booster.

Other therapeutics including **human growth hormone** and **palifermin** are also under investigation as immune-based therapies. These treatments are discussed in the TAG 2007 Pipeline Report; little additional information has become available since that report was published.

#### 4.4.3 Therapeutic vaccines

Around 20 products are currently being tested as therapeutic vaccines, with the aim of augmenting immune responses against HIV. Therapeutic vaccines have a number of potential roles:

- Maintenance of immune function in people on failing antiretroviral therapy, or improving immune function in those with poor immunological responses to therapy despite viral suppression.
- Delaying the initiation of HAART, or allowing prolonged periods of treatment interruption without harmful viral rebound and immune activation.

A study of Merck's Ad5 vaccine, encoding only HIV Gag, in 114 individuals with long-term viral load suppression and CD4 cell counts above 500 cells/mm<sup>3</sup>, showed a very strong inverse correlation between Gag-specific CD4 responses and viral load rebound after treatment interruption (participants received three immunisations at months 0, 3 and 6, and interrupted treatment three months after the final immunisation). However the study showed no significant difference in viral load levels 16 weeks after treatment interruption between placebo and vaccine group, although a trend was evident in favour of the vaccine group<sup>192</sup>. There may be potential to improve on these responses with vaccine constructs that induce stronger CD4 responses.

### 4.5 Pathogenesis research

#### 4.5.1 Requirements for eradicating HIV infection

Eradication of HIV infection has proved impossible with currently available therapeutics due

190 Soriano-Sarabia N et al. HIV-hepatitis C virus co-infection is associated with decreased plasmatic IL-7 levels. AIDS 21: 253 - 255, 2007.

191 Levy Y et al. Sustained immunological efficacy of repeated r-hIL-7 doses in HIV-1-infected patients: long-term follow-up of a phase I/II multicenter study. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, poster abstract 708, 2008.

192 Schooley R et al. Therapeutic accination with a Replication Defective Adenovirus Type 5 HIV-1 gag Vaccine in a Prospective, Double-blinded, Placebo-controlled Trial (ACTG 5197). Conference on Retroviruses and Opportunistic Infections, Boston, abstract 87, 2008.

to HIV's ability to remain in a latent state in memory cells, potentially establishing a lifelong reservoir of infected cells.

Eradication remains a key scientific goal. In a plenary address to the XVII International AIDS Conference in 2008 Robert Siliciano stated three conditions for eradication of HIV:

- Halting ongoing HIV replication.
- Identification of all reservoirs of latent HIV infection.
- Identification of agents which can eliminate latent HIV infection.

Recent research supports the hypothesis that ongoing HIV replication is halted by a three-drug HAART regimen that contains a protease inhibitor or NNRTI, and that any residual viremia detectable by ultrasensitive assays is the product of latently infected cells<sup>193</sup>. Currently available drugs appear to be potent enough to suppress ongoing HIV replication indefinitely, provided that adherence is excellent.

The main reservoir of latent HIV infection is the long-lasting pool of memory T-cells, but the existence of latent infection in stem or progenitor cells of the monocyte/macrophage lineage cannot be ruled out, and further efforts are required in order to identify all the reservoirs of latent HIV infection in the body, and the pharmacological characteristics of the cell types that harbour latent HIV.

Methods must be developed to identify and rid the body of cells which harbour the HIV genome in a latent state. Activation of the cells harbouring latent HIV has been proposed as a means of eliminating HIV, but activation of the entire memory cell population would provoke unacceptable levels of cytokine production, leading to severe adverse effects. A high level of immune activation would also create many target cells for HIV infection, sustaining another cycle of HIV infection and latency. Screening is already underway to identify compounds that can activate latent HIV in currently identified reservoirs without adverse effects.

Substantial progress has been made since the early 1990s in mapping the reservoirs of latently infected T-cells, understanding the pathogenesis of HIV infection and maximising the suppressive potential of antiretroviral therapy.

Based on the evidence of the suppressive potential of HAART, greater investment in pathogenesis research has the potential to identify a means of curing HIV infection.

## **4.6 Strategic research**

### **4.6.1 A cautionary perspective: the SMART study**

Any discussion of research into treatment strategies needs to acknowledge that well-intentioned, apparently reasonable strategies may lead to unexpected, disappointing, and even dangerous results.

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<sup>193</sup> Shen L, Siliciano RF Viral reservoirs, residual viremia, and the potential of highly active antiretroviral therapy to eradicate HIV infection. J Allergy Clin Immunol. 2008 Jul;122(1):22-8. Review

This was abundantly clear in the findings of the SMART (Strategies for Management of Antiretroviral Therapy) trial, a large international study designed to examine the effects of structured treatment interruption in HIV-positive patients. Patients in the interrupted-treatment arm of the trial stayed off therapy while their CD4 count was above 350 cells/mm<sup>3</sup> and resumed when it fell to 250 cells/mm<sup>3</sup>; those in the control arm remained on continuous treatment. Designed to run for over nine years, the study was stopped after only two years, when an interim analysis found a 2.5-fold elevated risk of significant disease progression in patients on interrupted versus continuous treatment<sup>194</sup>. More recent evidence has, moreover, shown a “residual risk” for patients in the interrupted-treatment arm, resulting in higher rates of disease progression even after those patients had resumed continuous treatment<sup>195</sup>.

Clearly, the message is that unexpected therapeutic outcomes can confound expectations, and that in such a serious illness as HIV infection, the consequences can be severe. (The converse can also occur, as in the next section, “Monotherapy”.) Human clinical trials must always be designed and monitored to ensure, as far as is possible, the safety of the participants.

The major strategic question over the next ten years will be the question of when to start treatment. A major ‘when to start’ study protocol is currently in development, and recruitment is expected to begin in the second half of 2008.

#### **4.6.2 Treatment in primary infection**

It is still unclear if treatment during primary HIV infection can reduce the subsequent risk of disease progression or permit the emergence of broader HIV-specific immune responses.

The SPARTAC trial is a multicentre randomised study of Short Pulse Antiretroviral therapy in primary HIV infection. The study is fully recruited and results are expected in 2010. The study is being conducted at sites in South Africa, Uganda, Italy, Australia, UK, and Brazil. The study will provide information on the effect on subsequent disease progression of short pulse treatment given during primary infection and the first year after infection.

#### **4.6.3 Monotherapy: ritonavir-boosted PIs**

Contrary to expectation, studies have shown that ritonavir-boosted lopinavir (*Kaletra*) can lead to sustained viral suppression in considerable numbers of patients when used as monotherapy, with no accompanying NRTIs or antiretrovirals of any kind. These surprising results were first observed in a pilot study in 2003, in an inner-city US clinic where treatment access was an issue for many patients<sup>196</sup>.

Many studies have continued to investigate the longer-term consequences of this unorthodox strategy. Evidence has not been strong enough to suggest that *Kaletra* monotherapy could

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194 El-Sadr W et al. Episodic CD4-guided use of antiretroviral therapy is inferior to continuous therapy: results of the SMART study. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 106LB, 2006.

195 El-Sadr W et al. Re-initiation of ART in the CD4-guided ART interruption group in the SMART study lowers risk of opportunistic disease or death. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston. Abstract 36, 2008.

196 Gathe JC et al. Single drug HAART proof of concept study. Pilot study of the safety and efficacy of Kaletra (LPV/r) as a single drug HAART in HIV+ naïve patients. Interim analysis of subjects completing at least 24 weeks of a 48 week study. 43rd ICAAC, Chicago, abstract 2608, 2003.



stand as a viable alternative to standard triple-drug therapy, and one of the largest studies recently published found that monotherapy suppressed the virus in significantly fewer patients than triple-drug therapy (64% vs. 75% at 48 weeks).<sup>197</sup>

By contrast, other studies have found comparable rates of suppression in certain groups of patients – in particular, those who were switched to *Kaletra* monotherapy after achieving viral suppression on standard treatment.<sup>198</sup> (See also “Induction/Maintenance”, below.)

These findings raise many critical questions:

- Might it be possible to assure ongoing treatment success with mono- or dual therapy?
- How could such agents be identified?
- How can clinical trials of such strategies be conducted safely and ethically?
- How does one produce evidence that such a strategy has a reasonable likelihood of success that would justify exposing participants to the risk of drug resistance?
- Might therapy with fewer drugs be appropriate for the “maintenance” phase of an induction/maintenance strategy?

#### 4.6.4 Tuberculosis

**Tuberculosis** is one of the leading causes of death in people with HIV in sub-Saharan Africa and Asia, and even after initiation of ART remains a substantial cause of mortality and morbidity.

There are numerous technological needs for the management of TB:

- Point of care diagnostics to facilitate faster identification of smear-positive TB at primary health care level.
- Smear negative diagnosis.
- Drug susceptibility tests that can provide results within days, at low cost.
- An accurate test for exposure that can identify latent tuberculosis.
- Reduce the length of the induction phase and reduce the total length of TB treatment.
- Identify drugs for the induction and maintenance phases of treatment that do not interact with ART.
- Find a shorter, equally effective preventive regimen to replace 6-9 months of isoniazid.
- A preventive vaccine against TB that is effective in adults.

These needs and the current pipeline of technologies, together with existing research efforts to address them, are discussed in more detail in the 2008 Pipeline Report published by Treatment Action Group<sup>199</sup>.

197 Delfraissy JF et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naïve HIV-infected patients. *AIDS* 22: 385-393, 2008.

198 Pulido F et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. *AIDS* 22: F1-F9, 2008.

199 Treatment Action Group. 2008 Pipeline Report, ps 28-56.

Developments in TB diagnostics are being led by the Foundation for Innovative and New Diagnostics and the Stop TB Partnership's New Diagnostics working group.

The Global Alliance for TB Drug Development is working with public and private partners to expand the range of TB drugs. Seven agents are currently in human trials.

The Aeras Global TB Vaccine Foundation, a product development partnership, is partnering with academic institutions and industry to advance a range of TB vaccine candidates, three of which have entered phase II studies.

#### **4.6.5 Future research questions**

Future questions for clinical research will include, at the very least:

- When is the optimal time to start treatment?
- Will three-drug therapy remain the standard of care, or will it be possible to construct effective two-drug regimens that have equivalent potency and tolerability? Will the dual-NRTI 'backbone' remain a mainstay of therapy?
- What are the plausible ways in which newly emerging drugs could be combined? How are such potentially 'plausible' combinations to be determined?
- Can viral reservoirs and agents to clear latent HIV from these reservoirs be identified?
- What is the role of therapeutic vaccination or other immunotherapy in improving immune reconstitution or permitting safe interruption of therapy?
- How can trials be developed so as to test new paradigms safely and ethically in humans?
- What are the host genomic factors which drive efficacy and toxicity? How are these distributed across ethnic groups?
- How will aging manifest in the growing population of people on long-term suppressive HAART? What are the societal and treatment implications of this? Do particular treatment regimens impact this process to a greater or lesser degree? Are host factors determinants, and if so how? In particular, how will cardiovascular disease, hepatitis C coinfection and malignancies affect the population taking HAART over the next thirty years?
- In light of the unexpected results of the SMART and other trials, how can we ensure that unexpected risks are responded to with a minimum of harm to study participants?
- Conversely, given the unexpectedly positive outcomes of (e.g.) lopinavir monotherapy, how can we allow room for exploring unorthodox treatment strategies while still minimising their potentially serious risks?
- Lastly, and critically, how can these questions be investigated in a way that addresses the needs of both the developed and developing worlds?

## 5 **Diagnostics**

Diagnostic testing for HIV encompasses tests for the diagnosis of HIV as well as the monitoring of HIV-infected individuals. One of the most pressing diagnostic challenges is adapting tests commonly used in resource-rich settings for use in resource-limited settings. It is generally accepted that in order to be widely implemented, diagnostic tests should be inexpensive and able to be performed in settings that lack reliable electricity, water, storage facilities, transportation, or skilled labour<sup>200</sup>. Ideally such tests would be available for rapid, point-of-care use.

### 5.1 **HIV diagnosis**

In the United States, up to 25% of HIV-infected individuals do not know that they are infected<sup>201</sup>, and the percentage is probably substantially higher in resource limited settings. Identifying HIV infected individuals has the potential to improve their health outcomes and prevent the transmission of HIV. For these reasons, the CDC recently recommended universal HIV testing<sup>202</sup>. In order to implement universal screening, there is an ongoing need for more rapid, robust, and palatable testing methods. There are also select HIV-infected populations for whom routine testing is ineffective or suboptimal; such as infants, acutely infected individuals, and vaccine recipients.

The largest challenge in HIV diagnosis lies not in the technology, but in its delivery. Frequent stock outs of test kits are reported due to poor supply mechanisms and the lack of robust forecasting methodologies for rapid HIV test demand. Maintaining quality control in the conduct of rapid testing is also problematic; while tests may be suitable for use by a wide range of health care workers, the personnel trained to monitor correct use of the tests may be in short supply.

### 5.2 **Rapid antibody tests**

Optimal testing for HIV antibodies requires the use of ELISA testing in the laboratory setting, delaying the delivery of test results. Numerous rapid tests using whole blood, serum or saliva which show a visual reaction within 15-20 minutes and have sensitivity in excess of 98% have been developed, and are now widely used in developing countries<sup>203</sup>. Although the sensitivity and specificity of rapid tests are good, testing algorithms generally require confirmatory testing with either Western Blot or IFA<sup>204</sup>.

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200 Calmy A et al. HIV viral load monitoring in resource-limited regions: optional or necessary? Clin Infect Dis 44(1):128-34, 2007.

201 Branson B et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR 55 (RR14): 1-17, 2006.

202 Ibid.

203 Comprehensive information on the rapid HIV antibody tests available for procurement is available from <http://www.rapid-diagnostics.org/rti-hiv-com.htm>, a PATH-maintained website.

204 Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral and revised recommendations for HIV screening of pregnant women. MMWR Morb Mortal Wkly Rep 2001; 50(RR-19):1-85; & DHHS/CDC.

However, the use of a second rapid test from a different manufacturer on blood drawn from a different time point is now considered sufficient, and has been recommended as the standard of care in resource limited settings<sup>205</sup>. Adapting rapid tests in order to process samples such as saliva, collection of which is perceived to be pain free, seems to significantly increase the number of individuals that can be tested and the percentage who received their results<sup>206</sup>.

Because of the fact that the use of whole blood for HIV rapid testing can be problematic in some groups of persons such as children, newborns, immunocompromised and obese individuals in whom getting blood samples can be particularly difficult; and increase risk to patient and health care workers, there has been more emphasis on the use of alternate body fluids such as oral fluid and urine because their collection involves non-invasive techniques, unlike phlebotomy and fingertip pricking. This could be more adaptable in resource-poor settings where trained manpower, acceptability and collection devices may compromise HIV diagnostic initiatives.

However, the one currently FDA approved assay which uses saliva, appears to have unreliable specificity<sup>207</sup> which can lead to an unacceptably low positive predictive value, especially when used for universal screening of a low prevalence population. Ongoing refinement of these assays by a variety of companies seems to have potential to address these issues.

### **5.3 Infant HIV diagnosis**

HIV antibody tests do not provide a reliable diagnosis in children under 18 months due to the presence of maternal antibodies. Approximately half of infants infected with HIV are likely to die by the age of two without diagnosis and appropriate treatment<sup>208 209</sup>.

Treating HIV-infected infants with antiretroviral therapy (ART) as soon as possible —within the first six to 12 weeks of life —reduces early mortality by 75%, according to the results from the Children with HIV Early Antiretroviral Therapy (CHER) trial<sup>210</sup>. Thus, prompt infant HIV

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Quality assurance guidelines for testing using Rapid antibody tests waived under the Clinical Laboratory Improvement Amendments of 1988, [http://www.cdc.gov/hiv/topics/testing/resources/guidelines/qa\\_guide.htm](http://www.cdc.gov/hiv/topics/testing/resources/guidelines/qa_guide.htm))

205 World Health Organization. Rapid HIV tests: Guidelines for use in HIV testing and counselling services in resource-constrained settings. 2004.

206 Centers for Disease Control and Prevention. False-positive oral fluid rapid HIV tests--New York City, 2005-2008. MMWR 57(24):660-5, 2008.

207 Centers for Disease Control and Prevention, *ibid*.

208 Mbori-Ngacha D, Nduati R, John G, et al. Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: A randomized clinical trial. JAMA. Nov 21 2001;286(19):2413-2420.

209 Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. Oct 2-8 2004;364(9441):1236-1243

210 Violari A et al. Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) study. Fourth International AIDS Society Conference on HIV Treatment and Pathogenesis, Sydney, abstract WESS103, 2007.

diagnosis should be a major international priority.

The current gold standard for infant diagnosis is the use of nucleic acid testing (HIV DNA PCR). Increasingly, in resource-limited settings dried blood spots have replaced blood collection tubes (e.g., *Vacutainer*) to collect and transport samples for DNA PCR testing. This approach is technically simpler than RNA based methods, although as RNA-based viral load monitoring has become routine and more available, there may be role for HIV-RNA detection in infant HIV diagnosis. Either nucleic acid-based method requires a well equipped lab and a relatively well-functioning logistic network. In the US, only 45 to 79% of individuals receive conventional HIV testing results, but anecdotal reports from developing countries, suggest that a combination of increased stigma, limited transportation and communication options, and more migratory populations results in a substantially lower proportion of individuals returning for test results. This stresses the need for a point-of-care format for infant HIV diagnosis.

The Forum for Collaborative HIV Research reported on an international expert meeting in 2006 at which the landscape of infant HIV diagnosis was reviewed<sup>211</sup>.

Meeting participants made a series of recommendations on improving diagnostic methods in children:

- Evaluate immunological methods (CD4/CD8 ratio, CD4 count) for infant diagnosis.
- Evaluate rapid antibody testing protocols as a screening test in HIV-exposed infants.
- Establish when ELISA can be reliably used for diagnosis.
- Improve nucleic acid extraction from dried blood spots in order to increase throughput.
- Establish the role of ultrasensitive p24 antigen testing.
- Evaluate the potential use of RNA based assays for diagnosis and monitoring.
- Evaluate ways of improving automation and throughput of currently available assays.
- Refining appropriate timing of testing.

The meeting also agreed that extensive operational research is also required to improve infant diagnosis.

The implementation of dried blood spot testing has moved forward quickly since 2006, but significant operational challenges remain<sup>212</sup>, and the development of a testing methodology that can confirm HIV status at the point of care remains a high priority.

#### **5.4 Diagnosis of acute HIV Infection and HIV in vaccine recipients**

Many of the challenges inherent in infant HIV diagnosis are also relevant to acute HIV infection. Early in HIV infection there is a window of time before there are detectable anti-HIV

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211 Forum for Collaborative HIV Research. Pediatric HIV diagnosis & laboratory monitoring. November 2006.

212 Theo Smart. Early infant diagnosis. HIV & AIDS Treatment in Practice 100, January 2008. <http://www.aidsmap.com/cms1257210.asp>

antibodies. With modern assays this window is up to 4-6 weeks<sup>213</sup>. For all individuals being tested, but especially blood donors and for individuals who seek HIV testing because of recent risk factors, diagnosing acute infection in this window period is important. Preventing the transfusion of blood from these individuals is paramount, but identifying acutely HIV infected individuals is also important because these individuals tend to have high viral loads and are thought to be responsible for a disproportionate amount of HIV transmission<sup>214 215</sup>. In order to detect acute HIV many centres have implemented pooled nucleic acid testing<sup>216</sup>, which are expected to become positive 8 days prior to IgM-EIA; and there is increased marketing of so-called “fourth generation” assays, which detect both anti-HIV antibody as well as HIV antigen(p24) and are expected to become positive 5 days before IgM-EIA<sup>217</sup>.

Diagnosis of HIV infections in vaccine recipients is not yet a pressing clinical concern. However, if a successful vaccine elicits a humoral response to typical HIV antigens, it would be expected that vaccine recipients would have false positive rapid and/or EIA tests. Although this diagnostic dilemma would represent the consequence of significant progress, it would potentially require whole new algorithms for HIV diagnosis, much in the same way that the Hepatitis B vaccine did for Hepatitis B. The NIH has already issued an announcement (BAA-NIAID-DAIDS-NIHAI2008027) to begin to work on this problem. Hopefully technology that is developed to diagnosis HIV in infants can be translated to solve this diagnostic dilemma as well.

### Further research questions

- Current modelling finds a wide range of estimates for the proportion of new infections attributable to individuals in primary infection<sup>218 219</sup>. What further research needs to be done to define the extent to which primary infection is responsible for new HIV infections?
- Current fourth-generation assays may provide a positive result within 15 - 20 days of exposure. How much public health value is there to developing assays that can reduce the ‘window period’ further? How feasible would it be to develop such assays? Are such assays primarily research tools for use in trials of PrEP and topical ARV products, or could such assays offer a new HIV prevention tool for use by individuals and community-based prevention workers? How might individuals use these assays?

213 Fiebig EW et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003 Sep 5;17(13):1871-9.

214 Wawer MJ et al. Rates of HIV-1 transmission per coital act by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 191: 1403 – 1409, 2005.

215 Pinkerton SD et al. How many sexually-acquired HIV infections in the USA are due to acute-phase HIV transmission? *AIDS* 21: 1625 – 1629, 2007.

216 Stramer SL et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. *N Engl J Med* 351(8):760-8, 2004.

217 Fiebig, *ibid*.

218 Wawer MJ et al. Rates of HIV-1 transmission per coital act by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 191: 1403 – 1409, 2005.

219 Pinkerton SD et al. How many sexually-acquired HIV infections in the USA are due to acute-phase HIV transmission? *AIDS* 21: 1625 – 1629, 2007.

## 5.5 CD4 counting

A major challenge in HIV diagnostics is the development of affordable tools for monitoring HIV infection and antiretroviral treatment in resource-limited settings.

In settings where CD4 monitoring is not available, treatment must be initiated on the basis of clinical staging. WHO has recommended that access to CD4 counting should be prioritised in national treatment scale-up. In patients receiving ART, a recent study in Uganda showed a trend towards superior outcomes in those who received regular CD4 cell monitoring as opposed to clinical monitoring alone<sup>220</sup>.

The Forum for Collaborative HIV Research has reviewed the landscape of monitoring technologies in a number of meetings and publications, with a particular focus on technology transfer and the development of new monitoring technologies that will be suitable for use in resource-limited settings.

In 2005 the Forum reported on new developments in CD4 counting, highlighting alternatives to flow cytometry, the current standard of care in the developed world<sup>221</sup>. Flow cytometry requires expensive dedicated equipment and a high level of training as well as excellent laboratory quality control. These characteristics make the technology unsuitable for use outside reference laboratories or research institutions in many developing countries.

CD4 counting assays currently undergoing evaluation, or already in use in developing countries include<sup>222</sup>:

### 1. Manual bead based technologies

- Dynal Manual Dynabeads Dynal® T4 Quant Kit
- Beckman Coulter cytosphere kit (Coulter® Manual CD4 Count Kit<sup>1-4</sup>)

### 2. Flow Cytometry systems that require minimal technical input

- Guava Easy Cd4<sup>223</sup>
- BD FACSCount
- Point Care (no peer reviewed publications)
- CD4 Select (uses same equipment as machinery for complete blood counts)<sup>224</sup>

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220 Coutinho A, Mermin J, et al. Utility of Routine Viral Load, CD4 Cell Count, and Clinical Monitoring among HIV-infected Adults in Uganda: A Randomized Trial. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 125, 2008.

221 Forum for Collaborative HIV Research. Transfer of HIV monitoring technologies into resource-poor settings: moving the field forward. Report of a Forum workshop. May 2005.

222 Baum, Linda L; Crowe, Suzanne; Landay, Alan L. Advances in CD4 cell enumeration in resource-poor countries. Current Opinion in HIV & AIDS. 2(3):234-240, May 2007.

223 Spacek LA et al. Evaluation of a low-cost method, the Guava EasyCD4 assay, to enumerate CD4-positive lymphocyte counts in HIV-positive patients in the United States and Uganda. J Acquir Immune Defic Syndr 41: 607-610, 2006.

224 Srithanaviboonchai K et al. Novel low-cost assay for the monitoring of CD4 counts in HIV-infected individuals. J Acquir Immune Def Syndr 2008;47(2):135-139.

### 3. Flow Cytometry based systems that require operator input/flow cytometry skill

- Beckman Coluter flow cytometry(FL, USA) (FlowCare, PLG CD4)
- Becton Dickinson, (Multiset, SP Tetraone)
- Partec (CyFlow™, CyFlow SL Blue , CyFlow Counter®/ CyFLOW(Green)

All the abovementioned share similar limitations: relatively high capital costs (ranging from \$2,000 to \$45,000) and unit costs (\$8 - \$20 per test), and in several cases, low throughput and labour intensive.

The costs of a variety of CD4 and viral load assays have been reduced as a result of negotiations between manufacturers and the Clinton Foundation, giving countries the opportunity to enter into leasing arrangements that charge on a per-test basis without the need for up-front capital investment.

However, very basic limitations of laboratory capacity such as unreliable electricity supply, lack of staff with sufficient education to receive training, poor supplier support, distance of health facilities from laboratories and lack of reliable transport for materials, will continue make CD4 counting and viral load testing difficult to implement outside highly resourced facilities with skilled laboratory personnel.

In view of these limitations a number of point- care assays designed to give rapid results are also being investigated, many with support from a Gates Foundation-funded CD4 Initiative based at Imperial College of London<sup>225</sup>:

- A microchip-based assay<sup>226</sup>: The system uses a standard epifluorescence microscope and commercial digital image processing software, but the authors of the study say that a system using a simple light-emitting diode (LED) and battery power would be feasible, and is currently under development by LabNow.
- Zyomyx: quantitative biochip-based assay due for external validation early in 2009.
- Inverness/ClonDiag assay, uses a CCD imager to image CD4 cells isolated in an array.
- BeckmanCoulter: semi-quantitative assay, three potential technology strategies currently under investigation.
- Burnet Institute / Duke and Rush University: semi-quantitative lateral flow device, final prototype due to enter clinical studies in early 2009.
- Cornell University: liposomal-based lateral flow assay; dye-carrying liposomes that are stable at high temperatures will bind to CD4 receptors within the assay. Timescale unknown.

The CD4 Initiative hopes that at least one successful assay will be available by 2010.

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<sup>225</sup> Personal communication from the CD4 Initiative.

<sup>226</sup> Rodriguez WR et al. A microchip CD4 counting method for HIV monitoring in resource-poor settings. *PLoS Medicine* 2: e182, 2005.



The weakness of point-of-care assays is likely to be their relative insensitivity; they may be unable to quantify moderate changes in CD4 count indicative of treatment failure, and may have greater value in determining when a patient needs to start treatment. More work is needed in order to determine what sort of assays will be required in order to support treatment switch decisions.

#### **Further questions:**

- How sensitive do point of care CD4 assays need to be? Are they only needed for staging individuals for treatment initiation, or for monitoring for treatment failure too?
- What is the relative need for point of care versus more sensitive assays likely to be in the medium term?

### **5.6 Viral load testing**

Viral load testing has been at heart of the revolution in HIV management in the developed world over the past 12 years, allowing clinicians to define a viral load threshold of 50 copies/ml as the target for antiretroviral therapy.

New assays are desirable in the developed world only to the extent that clinical research uncovers new targets to aim for, and in this respect, assay development is likely to be driven by future discoveries about HIV persistence and eradication. If, for example, research were to show that a combination of strategies could eradicate HIV from the lymphoid tissue, assays which could measure HIV DNA levels would be required.

For now, there is no evidence that the current cut-off point or current technologies are inadequate to meet clinical needs.

Current FDA-licensed assays are:

- Roche COBAS<sup>R</sup> Amplicor PCR version 1.5 (using 3 different formats: manual, manual extraction and COBAS (comprehensive bioanalytical system) amplification and detection , COBAS Ampliprep/COBAS Amplicor (Roche Molecular Systems, Branchburg, NJ)
- Roche COBAS<sup>R</sup> Taqman<sup>R</sup>
- Bayer/Siemens Versant bDNA
- bioMerieux Nuclisens HIV-1 QT assay (bioMerieux Inc, Boxtel, Netherlands)
- Abbott RealTime

These assays have subtle differences which are reflected in their performance profiles<sup>227 228</sup>. Although the assays have comparable performance across HIV sub-types, results are not strictly comparable between assays; results may vary by as much as 0.4log, requiring the consistent use of one test in monitoring patients or running a clinical trial.

In the developing world, new and affordable viral load assays are urgently needed. Current assays require a high level of training and laboratory facilities, and are expensive, making them unsuitable for use in most resource-limited settings. Given these obstacles, WHO does not currently recommend viral load testing as a priority for implementation. While such an approach may be cost-effective in the short term, there is grave concern that without viral load monitoring it will be impossible to detect early virologic failure resulting in a future epidemic of drug resistant HIV, and has been characterised as akin to “running with scissors”<sup>229</sup>.

Several alternatives to PCR are currently being used or tested; their chief advantages and disadvantages, as described by Susan Fiscus and colleagues<sup>230</sup>, are:

- Ultrasensitive p24 heat-denatured antigen assay: can be used for paediatric diagnosis, but still not validated for adult use; runs on same platform as ELISA, high throughput.
- Reverse transcriptase measurement: Caviidi’s ExaVir assay is already available at a discount through the Clinton Foundation; takes three days to run a test, but simple equipment. Detection limit of 2000 copies/ml<sup>231</sup>.
- Real-time PCR: Real-time assays are faster, have higher throughputs, larger dynamic ranges and fully automated extraction steps.

In early 2006 MSF organised a consultation among academics and workers in ARV rollout programmes to find a specification for an ideal viral load test for resource-poor settings<sup>232</sup>. They decided that it should require no more than a fingerstick’s worth of blood (about a tenth of a millilitre), a single cartridge into which a sample of blood could be inserted and which would give a result, that it should not require refrigeration, be able to be run on batteries, should not cost more than \$1000 per instrument and \$8 per test, should give a result within two hours and would be able to be done by a field health worker with 1-2 days’ training.

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227 Galli R et al. Comprehensive comparison of the VERSANT HIV-1 RNA 3.0 (bDNA) and COBAS AMPLICOR HIV-1 MONITOR 1.5 assays on 1,000 clinical specimens. *J Clin Virol* 34(4):245-52, 2005.

228 Berger A et al. Comparative evaluation of the Cobas Amplicor HIV-1 Monitor Ultrasensitive Test, the new Cobas AmpliPrep/Cobas Amplicor HIV-1 Monitor Ultrasensitive Test and the Versant HIV RNA 3.0 assays for quantitation of HIV-1 RNA in plasma samples. *J Clin Virol* 33(1):43-51, 2005.

229 Smith DM and Schooley RT. Running with scissors: using antiretroviral therapy without monitoring viral load. *Clinical Infectious Diseases* 46:1598–1600, 2008.

230 Fiscus SA, Cheng B, Crowe SA. HIV-1 viral load assays for resource-limited settings. *PLoS Medicine* 3 (10): e107, 2006.

231 Greengrass V., et al. Evaluation of the Caviidi ExaVir™ Load quantitative HIV RT load kit as an alternative HIV viral load monitoring test for use in Melbourne. Fourth International AIDS Society Conference on HIV Treatment and Pathogenesis, Sydney, abstract TUPEB019, 2007.

232 Calmy A, Ford N, Hirschel B, et al. HIV viral load monitoring in resource-limited regions: optional or necessary? *Clin Inf Dis* 44: 128-34, 2007.

Approaches to delivering a viable alternative include:

- SAMBA – nucleic acid-based test kit being developed by the University of Cambridge and Diagnostics for the Real World. A field study of this device is due to begin in Kenya in 2008.
- Siemens (now owner of Bayer): battery operated, hand-held nucleic acid-based testing device, being developed in collaboration with IAVI and NIAID.
- University of Maryland: anti-p24 antibody capture with an amplification step to improve on current ELISA-based p24 tests<sup>233</sup>.

The challenges associated with processing specimens in resource limited settings are common to many of the HIV diagnostic tests. PATH and others are investigating methods of making plasma sample processing easier and less dependent on cold-chain storage, and also investigating ways of easing the configuration of nucleic acid testing in order to make newer PCR-based tests easier and more cost-effective to use. Several groups are evaluating dried blood spots as a medium for use with HIV RNA assays. Indirect approaches such as using activation markers such as CD38 expression on CD8 cells on the flow cytometer are also being investigated.

Countries will need assistance in the arena of CD4 and viral load testing to ensure appropriate assay selection for their setting. Algorithms for appropriate use of these assays need to be developed in these settings, which may differ significantly from developed countries.

Further questions:

- What is the most clinically relevant cut-off point for a point of care viral load assay – 500 copies, 1000 copies or higher?
- Are point of care assays with relatively insensitive cut-offs of less relevance if HIV RNA extraction from dried blood spot testing can be improved for use with assays with a low limit of detection?
- Quality control of point of care assays: how much of an obstacle is quality control likely to prove?

## **5.7 Resistance testing**

In higher resource settings, HIV resistance testing has become commonplace, and current DHHS guidelines recommend HIV resistance testing at diagnosis, when starting therapy, and when failing therapy<sup>234</sup>.

Two basic types of resistance test are in use in the developed world:

- Genotypic: looks for specific mutations in the reverse transcriptase, protease or integrase gene associated with resistance to ARVs

<sup>233</sup> <http://www.ddcf.org/page.asp?pagelId=451>

<sup>234</sup> DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. January 29th, 2008

- Phenotypic: measures the drug concentration required to reduce viral replication. Virtual phenotyping relates genotypic information to prior data that matched genotype and phenotype, to produce an estimate of drug sensitivity.

Interpretation of genotypic data is increasingly complex and expert analysis is advisable. Genotypic interpretation is further complicated in non-B HIV subtypes, where resistance pathways can differ and where limited data are available on emerging patterns.

For the developed world, the key challenges in resistance testing will be optimising the use of genotypic tests in measuring changes in emerging targets, such as integrase and gag, and future viral proteins.

Another challenge with resistance testing is to determine the clinical significance of low-level drug-resistant variants that may persist below the level that can be detected with standard sequencing or phenotyping. Recent studies suggest that mutants at low concentrations may increase the risk of virologic failure with ART<sup>235</sup>. Existing methods for detecting mutant variants and low-concentrations include real-time PCR, Lig-Amp, oligonucleotide ligation, all point mutation assays directed at a limited number of codons.

In the developing world the use of resistance testing is currently restricted to surveillance and research, except in Brazil, South Africa, and Botswana, where testing is beginning to be incorporated in clinical care. It has been argued that, given the complexity and cost of genotypic testing, it should not be used to select second-line nucleoside analogues. Instead a public health approach seeks to sequence the nucleoside backbones that have least cross-resistance, reserving resistance testing for surveillance of emerging resistance patterns in the treated and untreated populations.

### **Further questions:**

- Is there a role for genotypic testing in developing countries if it is cheaper and easier to use, or should resources be devoted to other aspects of programme quality, such as adherence support, patient follow-up and more durable, better tolerated first-line drugs?
- If surveillance detects an increase in transmitted drug resistance and a growing prevalence of resistance, does this affect the cost/benefit calculation?
- What are the characteristics of a cheaper and easier to use genotypic test? Possible avenues of research include the development of an affordable point mutation assay which screens only for specific mutations be a priority, and the evaluation of affordable sequencing techniques.

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235 Simen BB, et al.(2007) Prevalence of low abundant drug-resistant variants by ultra-deep sequencing in chronically HIV-infected antiretroviral-naïve patients and the impact on on virologic outcomes. *Antivir Ther* 12: S149

## 5.8 Tropism testing

The emergence of CXCR4-tropic virus in untreated individuals is associated with a significantly increase risk of disease progression, leading some to suggest that it should be studied further as a routine monitoring tool for HIV-positive patients<sup>236 237</sup>.

Exposure to CCR5 antagonists in patients with CXCR4-tropic virus or a mixed tropism population will lead to a shift to a CXCR4-tropic population, leading to failure of CCR5 antagonist treatment, but the only study of a CCR5 antagonist in patients with mixed tropic virus showed no negative effect on CD4 count, suggesting that in treated patients the switch is not harmful during short-term follow-up<sup>238</sup>.

A test to identify whether HIV is CCR5-tropic or not was licensed by FDA in 2007. The *Trofile* assay was developed by Monogram Biosciences in order to screen patients for CCR5-tropic virus prior to exposure to CCR5 antagonists.

A number of other companies, including Pathway Diagnostics and Invirion are also developing assays, but these remain unvalidated.

Current assays rely on a phenotypic approach to tropism assessment and cost in the region of \$1500, making them unsuitable for resource-limited settings. This means that CCR5 antagonists cannot be used with confidence in resource-limited settings.

- Are alternative, cheaper tropism testing methodologies a priority if drugs in the CCR5 antagonist class could be manufactured cheaply as second-line options for the developing world, or should these drugs be reserved for PrEP?

## 5.9 Genomics and pharmacogenomics

A number of human genetic polymorphisms have been associated with faster disease progression<sup>239</sup> and immunological response to antiretroviral treatment<sup>240</sup>.

Some polymorphisms have also been shown to predict an increased risk of drug side-effects. The most prominent of these is a polymorphism associated with abacavir hypersensitivity. Screening for the HLA B\*5701 haplotype is now common practice in Europe before commencing abacavir treatment, and has been shown to significantly reduce – although not eliminate – the risk of hypersensitivity in a randomised study<sup>241</sup>.

236 Daar ES et al. Baseline HIV type 1 co-receptor tropism predicts disease progression. Clin Infect Dis 45 :643 – 649, 2007.

237 Goetz MB et al. Prediction of disease progression by HIV coreceptor tropism in persons with untreated chronic HIV infection. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, abstract H-1027, 2007.

238 Mayer H et al. Safety and efficacy of maraviroc (MVC), a novel CCR5 antagonist, when used in combination with optimized background therapy (OBT) for the treatment of antiretroviral-experienced subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial. Sixteenth International AIDS Conference, Toronto, abstract THLB0215, 2006.

239 Lama J, Planelles V. Host factors influencing susceptibility to HIV infection and AIDS progression. Retrovirology 4:52, 2007.

240 Ahuja SK et al. CCL3L1-CCR5 genotype influences durability of immune recovery during antiretroviral therapy of HIV-1-infected individuals. Nature Medicine, advance online publication, March 30 2008.

241 Mallal S, Phillips E, Carosi G et al. HLA-B\*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008 Feb 7;358(6):568-79.

Other polymorphisms associated with side-effects of nevirapine, efavirenz and atazanavir have been identified, as have genes associated with an increased risk of lipoatrophy, lipid elevations and peripheral neuropathy during antiretroviral treatment.

### **5.10 Monitoring for toxicity while on ART**

In higher resource settings, significant effort and cost is involved with monitoring for ARV toxicity. This can involve monitoring blood counts, electrolytes, lactate, pancreatic enzymes, creatinine, hepatic function, and lipid profiles. This information is frequently used to guide therapy decisions. As more HIV therapy options become available in low resource settings, more attention will need to be paid, to these “basic” laboratory tests. In many cases there will be additional technological challenges in order to make this spectrum of laboratory testing available in an inexpensive, reliable, point-of-care format. Hopefully, effort spent developing systems to monitor ART toxicity will bolster laboratory infrastructure and benefit general health care in general in low resource settings.

Important point of care monitoring tests for the medium-term include:

- Creatinine clearance (tenofovir is contraindicated in patients with impaired renal function): testing for creatinine or creatinine clearance each require laboratory facilities and specimen transport networks that are challenging to implement in resource-limited settings. Is a point of care creatinine test feasible and necessary?
- Haemoglobin (AZT is contraindicated in patients with severe anaemia and may worsen mild anaemia): HemoCue, DHT meter and Jenway colorimeter each have their drawbacks; while the HemoCue test was most accurate and acceptable in a field survey in Malawi, it was also the most expensive<sup>242</sup>. A cheaper test for use in primary care in resource-limited settings would have significant health systems benefits.
- Liver enzyme monitoring is recommended after the initiation of nevirapine treatment but doesn't happen in many settings due to lack of laboratory capacity.

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242 Medina Lara A et al. Evaluation and costs of different haemoglobin methods for use in district hospitals in Malawi. J Clin Pathol. 2005 January; 58(1): 56–60.

## 6 Conclusion

### 6.1 Intellectual property and access to new technologies

The complex landscape of international intellectual property is beyond the scope of this paper, but a number of key points should be borne in mind.

Access to antiretroviral treatment in developing countries has been made possible in large part as a result of the ability of generic manufacturers in India and South Africa to develop inexpensive fixed-dose combinations, that enabled development, manufacture and distribution of these drugs to many low- and middle-income countries without violation of international intellectual property agreements.

Subsequent to the 2005 implementation of patent registration on medicines in India there have been a number of attempts to register antiretroviral patents (a patent application on the protease inhibitor atazanavir was rejected in 2007, for example), but in 2007 the Indian High Court upheld the provision of India's 2005 Patents Act that grants patents only on innovations and not on products that are derivative of other compounds. The decision has permitted further development of affordable generic versions of antiretroviral medicines such as atazanavir, and has been interpreted as permitting the continued development of generic versions of second-line drugs.

The Indian High Court decision related only to that clause of the Indian Patent Act that covers new formulations of existing products or known substances. In 2008 an Indian patent was granted covering raltegravir, the first integrase inhibitor to be licensed in the US and Europe.

The future interpretation of intellectual property law and the actions of patent holders towards developing countries will critically affect access to antiretroviral drugs for decades to come, and innovative mechanisms are needed to guarantee access to affordable, safe and effective drugs whilst safeguarding scientific innovation.

Patent pooling has been proposed for further safeguarding and expanding access to medicines in developing countries, as have prize funds.

In the field of prevention technologies there has been widespread licensing of products from the private sector to product development partnerships, together with the promise of Advance Market Commitments for vaccine development.

## APPENDIX 1

**Trials of Preventive HIV/AIDS Vaccines Worldwide** (January 2008). Table reproduced courtesy of the AIDS Vaccine Advocacy Coalition

Protocol #	Start Date	Sponsor , Funder, Developer	Trial Site(s)	Number of Participants	Vaccine(s)	Clade
<b>PHASE III</b>						
RV 144	Oct-03	USMHRP, MoPH Thailand, Aventis, Vaxgen	Thailand	16,402	Prime: canarypox viral vector with <i>env</i> and <i>gag-pol</i> Boost: Env protein (gp120 subunits)	B A/E
<b>TEST-OF-CONCEPT</b>						
The two trials that follow, HVTN 503 and 502, stopped enrollment and immunizations, September 2007. Follow-up and data collection continue. For more information visit: <a href="http://avac.org/pr_step_study.htm">http://avac.org/pr_step_study.htm</a> .						
HVTN 503 (Phambili)	Feb-07	SAAVI, HVTN	South Africa	3,000	Adenovirus vector with <i>gag, pol, nef</i>	B
HVTN 502/ Merck 023 (Step study)	Dec-04	DAIDS, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica	801	Adenovirus vector with <i>gag, pol, nef</i>	B
<b>PHASE II</b>						
HVTN 204	Sep-05	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica	480	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	A, B, C
<b>PHASE I / II</b>						
EV 03/ANRS Vac20	June-07	European Commission, ANRS	UK, Germany, Switzerland, France	140	Prime: DNA vaccine with <i>env</i> plus <i>gag, pol, nef</i> Boost: NYVAC-C	C
HIVIS 03	Dec-06	MUCHS, Karolinska Institute, SMI, Vecura, USMHRP	Tanzania	60	Prime: HIVIS DNA with <i>env, gag, rev, RT</i> Boost: MVA-CMDR with <i>env, gag, pol</i>	A, B, C, A, E
RV 172	May-06	NIH, USMHRP, VRC	Kenya, Uganda, Tanzania	324	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	B A, B, C
<b>PHASE I</b>						
N/A	Dec-07	National Center for Disease Control and Prevention, the National Vaccine & Serum Institute, Peking Union Medical College Hospital	China	36	Replicating smallpox vector with HIV gene inserts	
<a href="#">HVTN 070</a>	Oct-07	NIAID, HVTN, UPenn/Wyeth	US	120	PENNVAX-B alone, in combination with IL-12, or with 2 different doses of IL-15	B
<a href="#">IAVI C004 / DHO-614</a>	Oct-07	Rockefeller University, ADARC, Bill and Melinda Gates Foundation, Ichor Medical Systems, IAVI	US	40	ADVAX e/g + ADVAX p/n-t, by Ichor TriGrid™ in Vivo Electroporation	C
HVTN 072	Aug-07	NIAID, HVTN, VRC	US	17	DNA and Adenovirus 5 or 35	A



					vectors, all with <i>env</i> in varying prime-boost combinations	
HVTN 071 [As of Sept 07 enrollment and vaccinations have been discontinued]	Jul-07	NIAID, HVTN, Merck	US	35	Adenovirus 5, vector with <i>gag</i> , <i>pol</i> , <i>nef</i>	B
DVP-1 [Enrollment paused]	May-07	St. Jude's Children's Research Hospital	US	20	Prime-boost regimen with <i>PolyEnv</i> , <i>EnvPro</i> , <i>EnvDNA</i>	A, B, C D, E
<a href="#">VRC 012</a>	May-07	NIAID, VRC	US	35	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	A
<a href="#">HVTN 067</a>	Apr-07	NIAID, HVTN, Pharmexa-Epimmune, Bavarian Nordic	US	108	DNA Vaccine EP-1233 and Recombinant MVA-HIV Polytope Vaccine MVA-mBN32, Separately and in a Combined Prime-Boost Regimen	
<a href="#">HVTN 069</a>	Nov-06	NIAID, HVTN, VRC, NY Blood Center, IMPACTA	US, Peru	90	Prime: DNA vaccine with <i>gag</i> , <i>pol</i> , <i>nef</i> + <i>env</i> Boost: Adenovirus 5 vector with <i>gag</i> , <i>pol</i> + <i>env</i> (intramuscularly, intradermally, subcutaneously)	A, B, C
<a href="#">HPTN 027</a>	Oct-06	Makerere University, Johns Hopkins University, NIAID	Uganda	50	Canarypox viral vector with <i>env</i> and <i>gag-pol</i>	B
C86P1	Sep-06	SGUL, Richmond Pharmacology, Novartis Vaccines	UK	31	Prime: HIV gp140 with LTK63 Boost: HIV gp140 with MF59	B
<a href="#">VRC 011</a>	Apr-06	NIAID, VRC	US	60	DNA vaccine with <i>gag</i> , <i>pol</i> , <i>nef</i> + <i>env</i> or Adenovirus vector with <i>gag</i> , <i>pol</i> + <i>env</i>	A, B, C
<a href="#">HVTN 065</a>	Apr-06	NIAID, HVTN, GeoVax	US	120	Prime: DNA plasmid with <i>gag</i> , <i>pro</i> , <i>RT</i> , <i>env</i> , <i>tat</i> , <i>rev</i> , <i>vpu</i> Boost: MVA vector with <i>gag</i> , <i>pol</i> , <i>env</i>	B
HVRF-380-131004	Mar-06	Moscow Institute of Immunology, Russian Federation Ministry of Education and Science	Russian Federation	15	VICHREPOL with polyoxidonium adjuvant	B
IAVI D001	Feb-06	IAVI, Therion	India	32	Modified vaccinia Ankara (MVA) viral vector with <i>env</i> , <i>gag</i> , <i>tat-rev</i> , <i>nef-RT</i>	C
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, USMHRP	Sweden	38	Modified vaccinia Ankara (MVA) viral vector with <i>env</i> , <i>gag</i> , and <i>pol</i> to volunteers from HIVIS 01	A, E
RV 158	Nov-05	USMHRP, NIH	US, Thailand	48	Modified vaccinia Ankara (MVA) viral vector with gp160, <i>gag</i> and <i>pol</i>	A, E
<a href="#">HVTN 063</a>	Sep-05	DAIDS, HVTN, Wyeth	US, Brazil	120	Prime: Genevax Gag-2692 +/- IL-15 DNA Boost: Genevax Gag-2692 + IL-12 DNA or IL-15 DNA	B
<a href="#">HVTN 060</a>	Aug-05	DAIDS, HVTN, Wyeth	US, Thailand	144	Prime: Genevax Gag-2692 +/- IL-12 DNA adjuvant	B

					Boost: DNA plasmids with gag or RC529-SE and GM-CSF with <i>env</i> , <i>gag</i> , <i>nef</i>	
<i>EnvDNA</i>	May-05	St. Jude's Children's Research Hospital	US	6	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with <i>env</i>	A, B, C, D, E
<a href="#">VRC 008</a>	Apr-05	NIAID, VRC	US	40	Prime: DNA vaccine with <i>gag</i> , <i>pol</i> , <i>nef</i> + <i>env</i> Boost: Adenovirus vector with <i>gag</i> , <i>pol</i> + <i>env</i>	B A, B, C
RV 156 A	Nov-04	NIAID, HVTN, VRC, USMHRP, Makerere U.	Uganda	30	VRC-HIVADV014-00-VP alone or as a boost to VRC-HIVDNA009-00-VP	A, B, C
HVTN 050/ Merck 018	Jan-04	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru	435	Adenovirus vector with <i>gag</i>	B
<a href="#">HVTN 049</a>	Dec-03	DAIDS, HVTN, Chiron	US	96	Prime: DNA vaccine with <i>gag</i> , <i>env</i> attached to microparticles Boost: Env protein (oligomeric gp140) + adjuvant (MF59)	B
<i>EnvPro</i>	Jun-03	St. Jude's Children's Research Hospital	US	9	Recombinant Purified HIV-1 Envelope Protein Vaccine	D
ADARC: Aaron Diamond AIDS Research Center ANRS: Agence Nationale de Recherches sur le Sida (France) DAIDS: Division of AIDS EV: EuroVacc HVTN: HIV Vaccine Trials Network IAVI: International AIDS Vaccine Initiative MoPH: Ministry of Public Health MUCHS: Muhimbili University College of Health Sciences NIAID: National Institute of Allergy and Infectious Diseases				NIH: National Institutes of Health SAAVI: South African AIDS Vaccine Initiative SGUL: St. George's, University of London SMI: Swedish Institute for Infectious Disease Control UK MRC: United Kingdom Medical Research Council USMHRP: United States Military HIV Research Program VRC: Vaccine Research Council		

## APPENDIX 2

Reproduced from AIDS Vaccine Advocacy Coalition's Px Wire: April-June 2008: *HIV Prevention Research: A Comprehensive Timeline of Efficacy Trials* (2008)

### HIV PREVENTION RESEARCH: A COMPREHENSIVE TIMELINE OF EFFICACY TRIALS\*

2007	2008	2009	2010	2011	2012+
FHI Phase III trial of the vaginal microbicide Cellulose Sulfate gel for the prevention of HIV infection in women (Nigeria)  Trial stopped early—January 2007 Results announced July 2007	Phase III trial of acyclovir for the reduction of HIV infection in high-risk, HIV-negative, HSV-2 seropositive individuals (Peru, South Africa, US, Zambia, Zimbabwe)  Results announced February 2008	Phase III trial of a prime-boost (ALVAC-AIDSVAX) combination preventive HIV vaccine (Thailand)	Large-scale efficacy trial of a once-daily dose of oral tenofovir+ emtricitabine to prevent HIV infection in heterosexual men and women (Botswana)	Phase III trial of community mobilization, mobile testing, same-day results, and post-test support for HIV (South Africa, Tanzania, Thailand, Zimbabwe)	Large-scale efficacy trial to determine the effectiveness of two different HIV prevention strategies: once-daily oral tenofovir and once-daily oral tenofovir+emtricitabine in serodiscordant heterosexual couples (Kenya, Uganda)
CONRAD Phase III trial of the vaginal microbicide Cellulose Sulfate gel for the prevention of HIV infection in women (Berlin, India, South Africa, Uganda, Zimbabwe)  Trial stopped early January 2007 Results announced July 2007	Large-scale trial to evaluate the safety of male circumcision and its potential protective effect for HIV-negative female partners of HIV-positive circumcised males (Uganda)  Trial stopped enrollment and surgeries in December 2006. Results announced February 2008	Phase II/III trial of the vaginal microbicides BufferGel and 0.5% PRO 2000/5 gel for the prevention of HIV infection in women (Malawi, South Africa, Tanzania, US, Zambia, Zimbabwe)	Large-scale efficacy trial of a once-daily dose of oral tenofovir+ emtricitabine to prevent HIV infection in high-risk men who have sex with men (Ecuador, Peru, South Africa, US)		Phase III trial to determine the effectiveness of two antiretroviral treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples (Brazil, India, Malawi, Thailand, US, Zimbabwe)
Phase III trial of the female dapivirgin to prevent HIV infection in women (South Africa, Zimbabwe)  Results announced July 2007	Phase III trial of the vaginal microbicide Carraguard for the prevention of HIV infection in women (South Africa)  Results announced February 2008	Phase II trial to test the clinical and behavioral safety of a once-daily dose of oral tenofovir among HIV-negative men who have sex with men (US)	Phase IIB trial of the vaginal microbicide tenofovir gel for the prevention of HIV infection in women (South Africa)		
Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate—STEP study (Australia, Brazil, Canada, Dom. Rep., Haiti, Jamaica, Peru, Puerto Rico, US)  Trial halted immunizations, September 2007. Follow-up and data collection continue.	Study of different risk-reduction interventions for HIV vaccine trials—Project UNITY (US)	Large-scale efficacy trial of a once-daily dose of oral tenofovir to prevent HIV infection in injecting drug users (Thailand)			
		Phase III trial of HSV-2 suppression in serodiscordant couples (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)			
Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate—Phambili (South Africa)  Trial halted enrollment and immunizations, September 2007. Follow-up and data collection continue.					

