SUMMARY REPORT

The Promise and Perils of ARV-based Prevention:
A Dialogue of Informed Optimism and Scepticism

Satellite Session
5th IAS Conference on HIV Pathogenesis, Treatment and Prevention
19 July 2009
Cape Town, South Africa

Co-organizers:
AIDS Vaccine Advocacy Coalition
International AIDS Society – Industry Liaison Forum

Background

Despite a number of proven HIV prevention interventions and more than 25 years experience with this epidemic, more than 7,400 new infections occur every day – an estimated 2.7 million in 2007 alone. The limitations of existing prevention efforts have driven increasing interest in the potential of antiretroviral (ARV)-based products to supplement existing HIV prevention interventions.[1] These interventions could be delivered in a variety of ways: in pill form, as oral prophylaxis (referred to as pre-exposure prophylaxis or PrEP), or as the active compound in topical microbicides (which could be formulated and delivered in a number of ways, such as gels, foams, films, rings or diaphragms). Proof of concept using ARVs as a prevention intervention has already been established for vertical transmission, and observational data have also suggested the significant potential of antiretrovirals to reduce HIV transmission.

A number of clinical trials are currently underway to test ARV-based prevention interventions in different populations using a variety of delivery mechanisms and dosage strategies. However, as the title of this satellite makes clear, both the scientific community and civil society have raised a number of questions about the research, development, financing and implementation of ARV-based prevention interventions.

The International AIDS Society (IAS) and AIDS Vaccine Advocacy Coalition (AVAC) have co-hosted a number of meetings and conference sessions over the past several years aimed at

[1] The ARV-based prevention discussed in this satellite did not include the potential population-level impact of ART on HIV transmission and the course of the epidemic.

addressing the ethical, scientific and operational issues raised by PrEP and other ARV-based prevention modalities. This satellite session at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009) in Cape Town, South Africa, provided an opportunity for an informed dialogue on both the potential of ARV-based prevention and the challenges the HIV field must come to grips with if clinical trials demonstrate efficacy. It is important to note that, while safety and efficacy results of Phase III clinical trials of PrEP and topical, ARV-based microbicides will be available at the beginning of 2010, this approach remains an unproven, albeit promising new biomedical prevention tool.

Introduction

The session was structured as two complementary discussions among panellists and audience members, the first dealing with research and development issues and the second dealing with implementation challenges, should efficacy be proven. The focus of the session was to stimulate interactive discussion among panellists and session participants rather than follow a traditional format of presentations and Q&As. The session was co-chaired by Mitchell Warren (AVAC, USA) and Michael Rabbow (Boehringer Ingelheim/IAS-ILF Industry Co-Chair, Germany). This report is not intended to provided a detailed description of discussion, but rather highlight the major themes that emerged during the session, with a view to pushing the debate forward as part of the planning process that will need to happen, whatever the results of current trials.

Panel One: Future Directions in ARV-based Prevention Research

Shirin Heidari (Facilitator)	International AIDS Society, Switzerland
Carl Dieffenbach	National Institutes of Health, USA
Yasmin Halima	Global Campaign for Microbicides, USA
Sharon Hillier	Microbicide Trials Network, USA
Patrick Ndase	International Clinical Research Centre, USA
Ben Plumley	Tibotec, USA
Zeda Rosenberg	International Partnership for Microbicides, USA
Francois Venter	South African HIV Clinicians Association, South Africa

Panel Two: What if it works? Implementation Issues

Emily Bass (Facilitator)	AIDS Vaccine Advocacy Coalition, USA
Stephen Becker	Bill & Melinda Gates Foundation, USA
Samukeliso Dube	Global Campaign for Microbicides, USA
Yogan Pillay	Ministry of Health, South Africa
Cate Hankins	UNAIDS, Switzerland
Victor Lakay	Treatment Action Campaign, South Africa
Helen Rees	Reproductive Health & HIV Research Unit, South Africa
Jim Rooney	Gilead Sciences, USA

Mitchell Warren welcomed participants and opened the session by providing an update on the current status of ARVbased prevention research (see Figure 1). Additional information on PrEP, microbicides and other prevention research is available on the AVAC website at http://www.avac.org/ht/d/sp/i/176/pid/176.

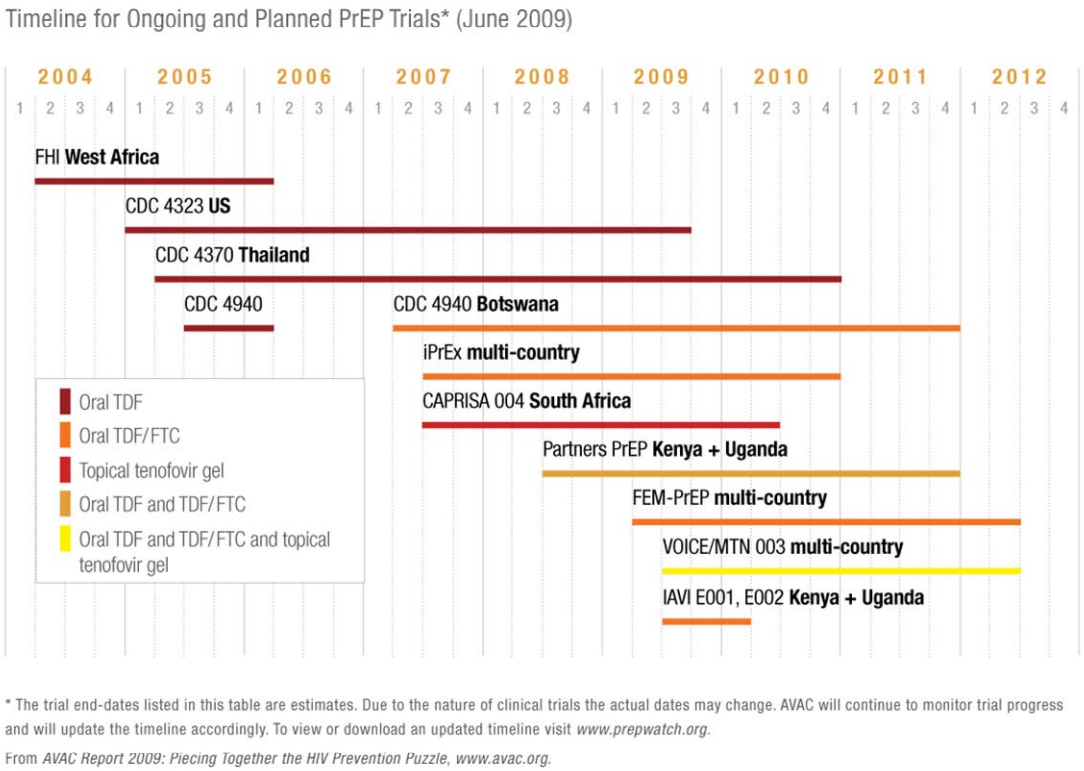

Figure 1: The Current Research Landscape for ARV-based Prevention Interventions

Michael Rabbow briefly outlined the role and composition of the IAS-ILF (a multi-stakeholder forum of investigators, industry, clinicians, civil society organizations and normative agencies), which focuses on strengthening clinical research investment in resource-limited settings, with an emphasis on the role and responsibilities of industry as sponsors and supporters of research. Additional information on IAS-ILF is available online at International AIDS Society - Industry Liaison Forum. Michael reminded satellite participants that key questions for this promising research area include how ARV-based prevention could be integrated into HIV services in resource-limited settings, how to make the most strategic use of this intervention, and what additional studies and considerations need to be established to make the best use of this intervention, should efficacy be proven.

More, Different, Better: The Research Agenda

Yasmin Halima and Sharon Hillier stressed the need to ensure a sustainable and expanded research and development pipeline for PrEP and ARV-based microbicides, particularly given the potential they may provide for an effective, female-controlled prevention tool. Both they and other panellists noted that this research agenda will need to be driven primarily by the public sector and private foundations such as the Bill & Melinda Gates Foundation, the US Centers for Disease Control and Prevention, and the US National Institutes of Health; the 'value proposition' as one industry representative noted, is not the same in the biomedical prevention field as it is in treatment, and no companies currently have an ARV-based prevention research and development (R&D) pipeline, although this may change as this field is still relatively young. Both industry and non-industry panellists noted that rethinking the role of industry in research on ARV-based prevention interventions - as supporters of

research and suppliers and licensers of the active compound rather than as the primary driver and funder of research – will be important given that commercial prospects and liability issues remain a serious concern for the industry as a whole. Sharon Hillier also stressed the need to break down the 'silos' that currently exist among donors, companies, investigators (both clinical and social science researchers) and regulators to accelerate and expand the development and approval of both rectal and vaginal microbicides.

Carl Dieffenbach stressed the need to prove efficacy in the current generation of ARV-based prevention modalities as PrEP and microbicides, then move to bridging studies (using pharmacological data to evaluate optimal dosage and timing), after which strategies and guidance must be developed on how to make these interventions available to populations at highest risk for HIV infection. Panellists stressed the need for innovation in this operationally challenging and costly field of research, where large cohorts are required and correlates of protection must be factored into establishing trials sufficiently powered to answer key questions about efficacy, tolerability and safety.

Suggested future directions in ARV-based prevention research included:

- innovative clinical trial design (e.g., by comparing oral prophylaxis to a topical microbicide in different arms of the same trial)
- evaluating differing formulations and delivery systems, such as developing a long-lasting injectable form of the drug (as Tibotec is currently doing with a compound in pre-clinical evaluation)
- evaluating efficacy on various modes of transmission, such as rectally applied microbicides
- evaluating compounds with differing potency and resistance profiles.

While Gilead is the only company that currently has products in Phase III clinical trials (including microbicide trials), Tibotec has a compound (TMC-278) in an injectable format in pre-clinical testing and has licensed one of its approved compounds to IPM. Pfizer's maraviroc is also being considered for evaluation given its high plasma concentrations in male and female genital tracts. Zeda Rosenberg noted that IPM has a number of partnerships and licensing agreements to develop the second generation of ARV-based microbicide clinical trials with new agents and dosing strategies.

Panellists noted that tolerability and safety issues will be a key concern, as these compounds are being tested in large, healthy cohorts, often in highly stigmatized and vulnerable populations. A strong pharmacovigilance system should be in place to report adverse events, in both pre and post-marketing phases, along with pre-established referral mechanisms to appropriate testing, counselling and treatment services for trial participants who screen out due to testing HIV positive during the trial.

Both panellists and audience members agreed that modelling studies and algorithms are needed to supplement clinical trial data in order to identify the greatest potential impact of these interventions among different populations, using a variety of dosage strategies (e.g., intermittent use among key populations such as sex workers, men who have sex with men [MSM] and heterosexual women in high-burden countries).

In addition, both panellists and audience members reinforced the need for social science research to help provide information on how best to deliver ARV-based intervention most strategically, and for maximum individual and population-level benefit, taking into account the complex social, cultural, legal and behavioural factors that affect vulnerability to HIV infection and access to prevention services.

The Regulatory Quandary: Liability, Approval and the Policy Environment

There is no clear consensus on what level efficacy results from current Phase III trial results would be convincing enough to warrant regulatory submission for approval of a new indication. A straw poll at the satellite session indicated that most participants felt at least 50 – 60% efficacy should be demonstrated (similar to circumcision trial findings) before proceeding to regulatory approval, although some indicated that efficacy results as low as 30% could be sufficient.

Liability and indemnification remain major concerns for companies considering regulatory approval for a new indication, as is the inevitable pressure to make their products available at minimal cost. Researchers and advocates stressed the need for companies to provide support to ARV-based prevention research despite the disincentives (such as providing a drug for clinical trials free of charge). The possibility was also raised by Jim Rooney that innovator companies may not need to seek regulatory approval for PrEP (depending on the requirements of specific regulatory agencies), given that many requirements of regulatory authorities will already have been met in the original submission for the compound as a treatment intervention. Regulatory approval may not be required for a change in indication (e.g. for oral prophylaxis) but it will be required for topical microbicides, and regulatory issues are compounded by the number of agencies and variations in expectations and submission requirements from those agencies.

Stephen Hillier added that key considerations for industry include preparing for manufacturing scale-up, negotiating agreements with generic and brand-name manufacturers and distributors, agreeing on the lowest possible cost to increase availability, and developing trainings to ensure the product is marketed and delivered appropriately.

Panellists agreed that the research community, donors, civil society, industry and relevant UN agencies will need to plan in advance on how to proceed with respect to the complex and sometimes conflicting requirements of regulatory authorities. Cate Hankins emphasized that increasing the capacity for understanding the epidemic at the country level will help identify the populations for whom this would be a useful product (in combination with other behavioural and structural interventions), suggesting that country-level consultations be held to define where this intervention fits best and how to deal with the pharmacovigilance expectations of regulators.

There was consensus among satellite participants that work with regulatory authorities should begin well in advance of a formal submission, as there is little knowledge or expertise among regulators regarding ARV as a prevention intervention and therefore the expectations of regulators and policymakers are not clear, for example, on adverse events reporting and frequency of HIV diagnostic testing among individuals using ARV-based prevention interventions.

Access and Obstacles: The Roadmap to Implementation

The question of who will have access to ARV-based prevention interventions (if efficacy is proven) received significant attention in the discussion; participants seemed to agree that PrEP would have the most public health benefit as a targeted, strategically-timed intervention for populations at high risk for HIV infection (e.g., sero-discordant couples, sex workers). However, Francois Venter raised a number of questions about how this intervention would be funded and operationalized, including who would have access to it given the current challenges in ensuring access to basic prevention tools like condoms, and how it would be delivered. He reminded participants that most high-burden countries are falling well short of meeting existing treatment needs and raised questions about the extent to which the rhetoric about the preventive potential of microbicides and PrEP makes the field vulnerable given its striking lack of success to date.

Patrick Ndase stressed that implementation planning must include how to get the attention of policymakers by packaging PrEP in the right way: ensuring they have the best available evidence to make decisions about ARV-based prevention investments given resource limitations (e.g., modelling and cost-effectiveness studies as well as clinical data,). Other panellists agreed and added that the results of community consultations and analysis of demographic and epidemiological data should also be part of the package. Audience members suggested that taking a regional or broadly systemic approach with policymakers and regulators might help speed licensure and access, with several satellite participants noting that people will start using these products once efficacy is known without waiting for regulatory approval.

Panellists also agreed on the need to develop normative guidance and programme implementation strategies that ensure ARV-based interventions are effectively targeted and delivered as part of a comprehensive prevention package that includes counselling, condoms, and other socio-behaviour and structural interventions. Audience members tended to agree that these products should be dispensed in a health care facility, although the specifics of how these products should be delivered to have maximum impact on the epidemic, remains an outstanding question.

Participants stressed the need to work at the country level (a role it was suggested UNAIDS and WHO need to lead) with health care providers, community groups, people living with HIV (PLHIV) and policymakers to build relationships, communication channels and a 'roadmap for implementation'.

Truth and Consequences: Communications and Social Marketing

Few issues captured the attention of the audience as much as the need to develop consistent, accurate social marketing messages about the limits of ARV-based prevention interventions; both panellists and audience members agreed that managing expectations through careful communications and social marketing regarding both the risks and benefits of such interventions will be critical to its effectiveness and should be an integral part of implementation rollout. Circumcision rollout was cited both as both an example of good

practice and as a cautionary tale – depending on the country – of how policymakers and national programme managers need to be engaged and educated in advance on both the risks and potential benefits of biomedical prevention technologies.

Building relationships with local and national media in advance of programme implementation will be important to ensuring that accurate information about the benefits and risks of ARV-based prevention interventions are disseminated to the public and – most importantly – to key populations.

Show Me the Money: Financing and Long-Term Sustainability

The question of who will pay for an expanded and potentially costly range of ARV-based prevention interventions (whether PrEP or topical microbicides) was raised as a question but not discussed in detail. Yasmin Halima, among others, questioned why the cost question was raised as an impediment to ARV-based prevention interventions when this has not traditionally been the case with respect to treatment. Participants suggested that donors – particularly bilateral aid agencies – be engaged in discussion about the need to fund such interventions and the value and impact these interventions will have in combination with existing prevention interventions.

Securing the necessary support from policymakers, who will also be responsible for making financial decisions and providing them with accurate costing and cost-effectiveness analysis over the long-term, was also stressed.

The Way Forward

While there were few definitive answers to the range of questions raised during the course of the satellite, the active engagement and sometimes heated debate among participants served to further define the key challenges, opportunities and options for moving forward on the research, development and implementation agendas in this promising new field. Some of these activities - such as discussions between industry and regulators and among NGOs and other civil society actors – are already taking place. The IAS-ILF and AVAC hope that this and other sessions will place ARV-based prevention on the radar screen of regulators, policymakers, health care providers and civil society and will help move this intervention forward from promise to reality.

The webcast of this satellite is available online at Promise and Perils of ARV-based Prevention - A Dialogue of Informed Optimism and Scepticism.