IAS INDUSTRY LIAISON FORUM

22 FEBRUARY 2005, BOSTON

In Attendance

Joep Lange, Academic Medical Center and IATEC, Netherlands (IAS-ILF Co-Chair), Michel Kazatchkine, French Ambassador for HIV/AIDS and ANRS, France (IAS-ILF Co-Chair), Pedro Cahn, Fundación Huesped and IAS, Argentina (Meeting Co-Chair), Yasmin Halima, IAS-ILF, Switzerland/UK (IAS-ILF Forum Co-ordinator), Jacqueline van Tongeren, IAS-ILF, Netherlands (Meeting Organiser)

Terrence Blaschke, Stanford University, USA, Rob Camp, Treatment Action Group, USA, Ben Cheng, Collaborative Forum for HIV Research, USA, Myron Cohen, Chapel Hill, USA, Chris Collins, IAS, Switzerland/USA, Paul Coplan, International Partnership for Microbicides, USA, Geoff Cotton, Gilead Sciences, USA, Rob Dintruff, Abbott Laboratories, USA, Thomas Fischer, Boehringer-Ingelheim, Germany, Bob Grant, University of California, San Francisco, USA, Craig Hendrix, Johns Hopkins University, USA, John Idoko, Jos University Teaching Hospital, Nigeria, Amy Keller, GSK, USA, Dale Kempf, Abbott Laboratories, USA, Emilio Ledesma, BMS, USA, Louise Martin-Carpenter, GSK, USA, Veronica Miller, Collaborative Forum for HIV Research, USA, Richard Ogden, Pfizer, USA, Noam Perski, IAS, Switzerland, David Reddy, Roche, Switzerland, Renee Ridzon, Gates Foundation, USA, Lew Sibert, Tibotec, USA, Jean-Marc Steens, GSK, UK, Paul Stofels, Tibotec, Belgium, Babajem Taiwo, Northwestern University Chicago, USA, Randall Tressler, Pfizer, USA, Remko van Leeuwan, IATEC, Netherlands, Maria Vigneau, Roche, Switzerland, Chris Woodward, Abbott Laboratories, USA, Rainer Ziermann, Bayer, USA

Summary of IAS Industry Liaison Forum Meeting, 22 February 2005, Boston

The IAS Industry Liaison Forum (IAS-ILF) convened during the CROI meeting in Boston in February 2005. The discussion was planned to take further the outcome from the previous IAS-ILF meeting at ICAAC in September 2004, where ILF members agreed to prioritise pre-exposure prophylactic (PREP) research as a key priority for IAS-ILF. This decision was based upon the need and current investment in PREP research and to explore and develop consensus on scientific and ethical challenges to the development of PREP candidates and associated operational and capacity limitation.

The agenda for the discussion focused on (i) the scientific challenges to the development of effective pre-exposure prophylactic agents, in particular, understanding the virologic and pharmacological considerations for PREP, (ii) a review of the macaque data from the tenofovir (TDF) studies and (iii) development and contextual challenges facing industry and resource-poor countries in the emergence of PREP research and delivery.

The following is a summary account of the presentations and discussion that took place at the meeting.

Preventing Transmission of HIV, Myron Cohen, Director, Center for Infectious Diseases, University of North Carolina, Chapel Hill

Myron Cohen presented an erudite introduction to the determinants of transmission and prevention of HIV. He stressed the biological requirements for the transmission of HIV as determined by infectivity and susceptibility with infectivity requiring concentration of inoculum and influenced by phenotypic factors whilst susceptibility is influenced by hereditary and innate resistance and acquired immune resistance (Cohen and Galvin, Nature Microbiology Reviews, 2004)

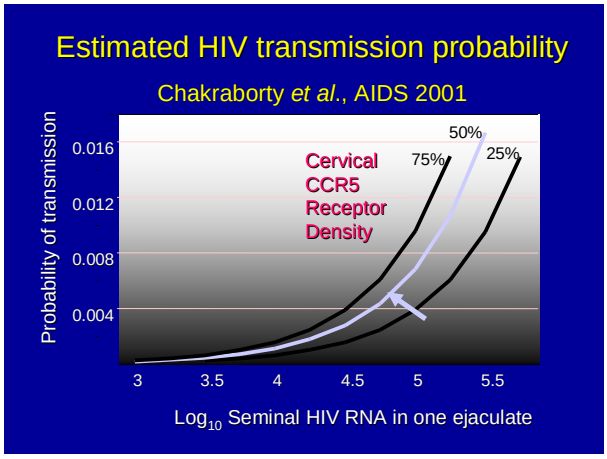
Routes of Exposure and risk of HIV infection

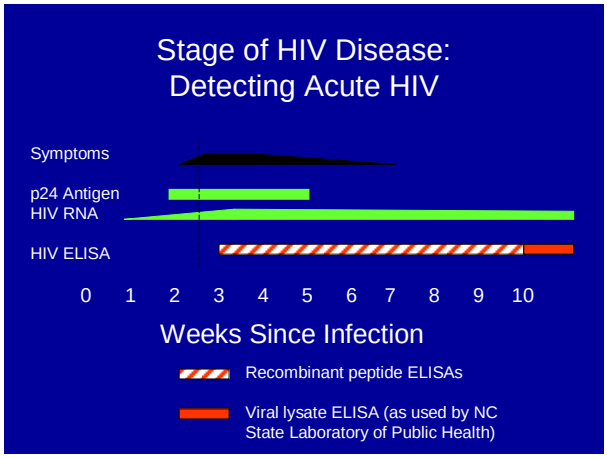
INFECTION ROUTE	RISK OF INFECTION
Sexual Transmission	
Female-to-male transmission	1 in 700 to 1 in 3,000
Male-to-female transmission	1 in 200 to 1 in 2,000
Male-to-male transmission	1 in 10 to 1 in 1,600
Fellatio?	0 (CDC) or 6% (SF)
Parenteral transmission	
Transfusion of infected blood	95 in 100
Needle sharing	1 in 150
Needle-stick	1 in 200
Needle-stick /AZT PEP	1 in 10,000
Transmission from mother to infant	
Without AZT treatment	1 in 4
With AZT treatment	less than 1 in 10

(Royce, Sena, Cates and Cohen, NEJM, 1997)

The important issue in explaining HIV transmission and the impact on the burgeoning epidemic in resource-poor countries is whether *amplified* transmission is critical to the spread of HIV and if so, if transmission is intermittently *amplified* by increased genital tract shedding and other factors such as

stage of disease and co-infections including sexually transmitted infections, malaria, helminthic infections and tuberculosis. According to data from the Rakai district, 'early' HIV patients are responsible for 43% of all HIV transmission in serodiscordant couples (Wawer et al., JID 2005 and Cohen)

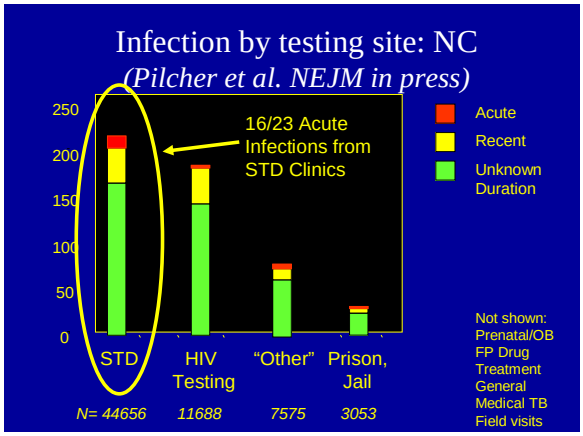


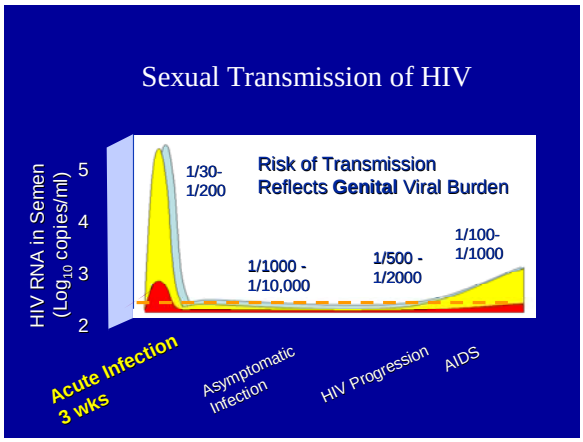


Estimated HIV transmission probability (Chakraborty et al, AIDS 2001)

The Chakraborty graph (AIDS 2001) of transmission from men to women confirms what we know that higher viral loads result in greater transmission. But more interestingly, the data further shows that women with the highest concentrations of co-receptor density are the most vulnerable to acquisition of HIV.

Of significant note is the timing of HIV testing and detection. HIV infection can be detected weeks before antibody tests become positive. The presence of HIV can be confirmed using tests that detect HIV directly in the blood, as early as 1-2 weeks after infection. Antibody tests however, can take one to nine weeks longer. As Dr Cohen noted, the big question is - do people show up for HIV tests during the first few weeks after infection? If not, the question of when different tests detect HIV is not significant. But if they do, we may be missing many of the HIV infections with our current testing practices that rely on HIV antibody detection alone.





Acute infection however, is difficult to detect in any given population, particularly those with limited health and prevention infrastructure. Interestingly, data from Lilongwe, Malawi involving 1,361 men screened in STD and Dermatology Clinics showed that almost half of the men had chronic HIV infection and of those reported antibody negative, 2% (28 men) in fact were found to have acute infection; this is a substantially increased level of infection then would normally be found. Only patients with STD were detected with acute infection (antibody negative and RNA positive) confirming the immutable relationship between STDs and HIV. (Pilcher et al AIDS, 2004)

STDs are critical to the phenomenon HIV transmission as they are known to increase HIV transmission by reducing physical and mechanical barriers, increasing HIV in genital lesions, semen or both, evoking a more infectious HIV variant and increasing the number of receptor cells or the density of receptors per cell.

Dr Cohen concluded by listing current research activity in HIV prevention, including:
- STD control, behavior change, condoms
- vaccines (trials ongoing)
- treatment of bacterial vaginosis
- topical microbicides (trials ongoing)
- the diaphragm (trials planned)
- male circumcision (trials ongoing)
- antiviral therapy (PREP, PEP and patients)
- societal and structural change: what are the incentives for safer sex?

Developments in pre-exposure prophylaxis, Bob Grant, University of California, San Francisco and Gladstone Institute of Virology and Immunology

Bob Grant outlined the profile of an ideal PREP agent as one that (i) does not require the risk of every contact be appreciated, (ii) can be female initiated, (iii) can be used without knowledge of partner, and (iv) does not have to be coordinated with sexual practices. Whilst the optimal mechanism of action is not known, it can be deduced that if free virions are the key vector of transmission, than action prior to integration may be ideal. Other mechanisms may be better if virus producing cells are the vector of transmission in which case the goal is to block “beach-head” infections in regional lymph nodes and systemic spread. Data from Tsai et al (Science, 1995) and Van Rompay et al (JID, 2001) showed protection from SIV with TDF. Tenofovir 20-30 mg/d by intramuscular injection prevented SIV infection in rhesus macaques, even if dosing started 24 hours after the virus inoculation. Limitations to extrapolating study outcomes include the fact that TDF dose was 6 times the human dose and viral dose is higher (5 x MID) than normally experienced by humans.

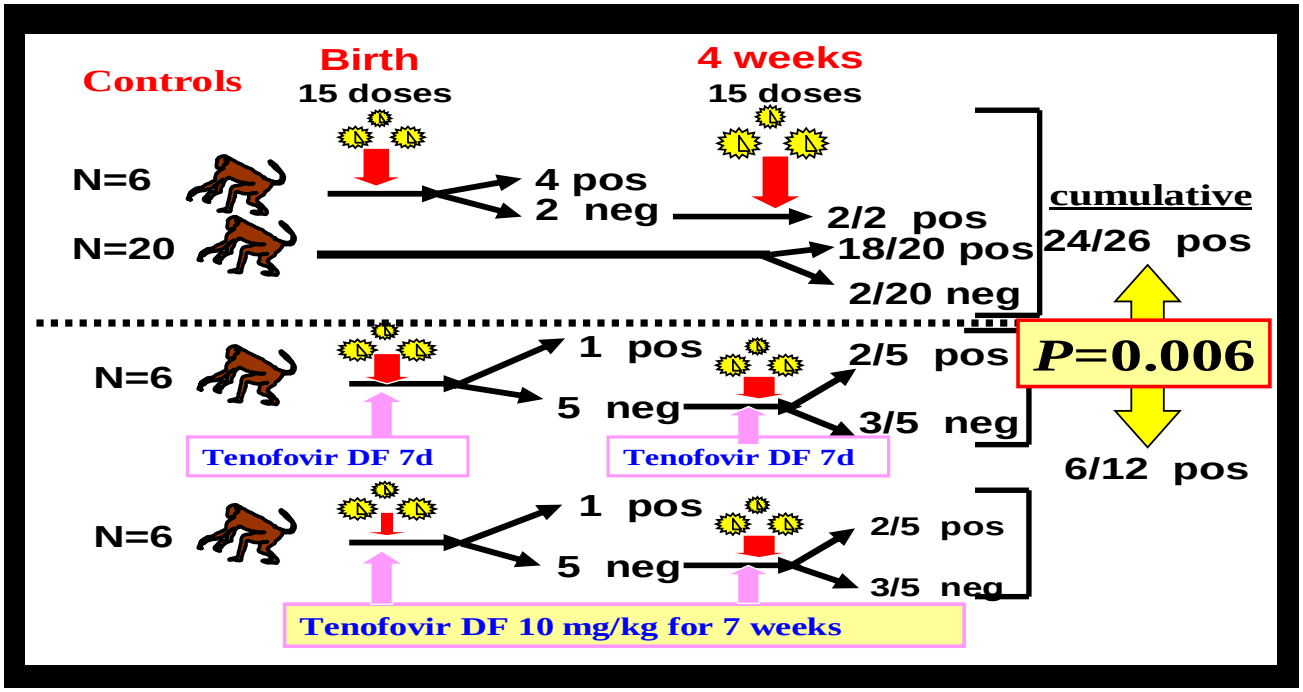
Van Rompay et al, JID 2001 - Partial Protection against TDF Resistant SIV

Table 4. Statistical analysis of protection against oral simian immunodeficiency virus (SIV) infection.

Group[a]	Infected	Protected	P^b
A + 12 historical control animals	16	0	—
B	1	3	.0035
C	2	2	.032
D	0	1	.059
B + C + D combined	3	6	.0005

Von Rompay (JV 2000) - TDF 30 mg/kg/d IM; Challenge with SIV RT K65R: 3/3 untreated control animals infected; 2/5 treated animals protected; 3/5 treated animals infected, but lower viral load and delayed disease progression.

Oral Tenofovir DF protects infant macaques against infection following repeated low-dose oral exposure to virulent SIV (Koen van Rampay, 2004).



Most recent data from the TDF animal studies presented at CROI 2005 showed that the benefit of TDF with repeated viral inoculum may in fact be compromised.

Chemoprophylaxis with Rectal Exposure in Macaques

Subbarao et al, 12th CROI, 136LB

	Number of Challenges					*Risk/*
	1	*2*	*6*	*>8*	*>11*	*Challenge*
	Number of Infections					
Placebo (N=4)	2	3	3	4	4	~50%
Daily TDF (N=4)	0	0	2	3	4	~15%
Weekly TDF (N=4)	0	0	2	3	4	~15%

TDF lowered the risk per viral challenge,
Which is key for MTCTP and PEP,
But the "per contact" benefit was overcome
with repeated challenges.

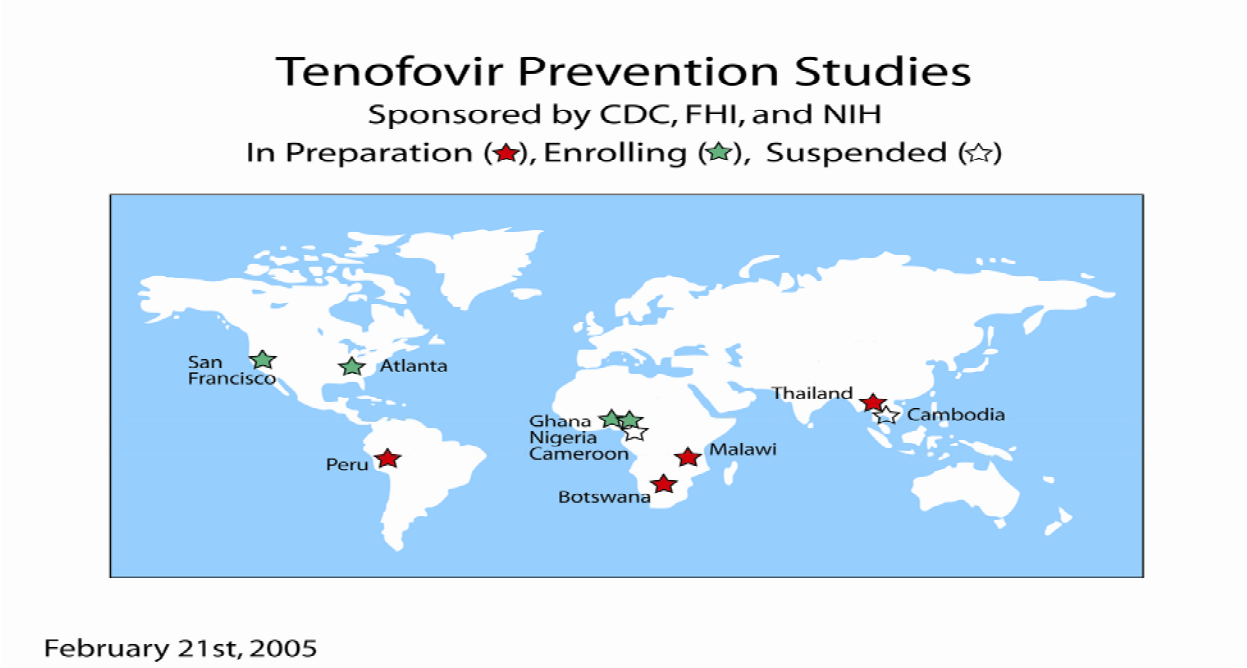
In the comparison of primate data to human application there are notable caveats including the consideration of different profiles of transmission as well as dosing and viral challenges.

Limitations of Non-human Primate Models of Chemoprophylaxis

	SIV	**HIV-1**
Transmitted by sex	no	yes
(atraumatic mucosal application ≠ sex)		
Virus dose sufficient to infect:	50-100%	0.1 to 5%
TDF dose used	4-30mg/kg	4mg/kg
Viral challenges	few	many

The 50% efficacy data in monkeys can be seen as either positive or negative. TDF PREP could be more effective in humans with less virus dose and that TDF dose is better known. Since TDF also has a long intracellular half-life it allows for a more forgiving regime if a dose is missed. However, TDF PREP can also be perceived to be less effective in humans due to poor adherence and behavioral differences.

Dr Grant outlined the planned clinical trials of tenofovir chemoprophylaxis which will
- enroll HIV-1 uninfected persons at risk
- randomize 1:1 to daily oral tenofovir 300 mg/d versus placebo
- at least one year follow-up for: toxicity, seroconversion, adherence, drug resistance, risk behavior and post chemoprophylactic effects on viral load and CD4 counts



All participants will receive standard prevention interventions including counseling, condoms, STI diagnosis and treatment. The aim of the study is learn if TDF has additional protective benefit. Participants will provide consent in a language that they understand and all studies have involved community consultation although more communication with communities on research remains essential.

Population and situational factors that bear on PREP and justify research in populations most impacted by HIV

- pharmacokinetics (body size, genetics); adherence patterns
- different viral exposures by risk group; drug penetration, target cell type, efficiency of transmission, frequency/patterns of exposure
- temperature and stability of drug supply
- impact of grey and black markets for drugs
- viral types and subtypes
- social and behavioural factors

Although there are concerns regarding drug resistance for any use of single-agent in the case of infection, the drug resistance profile of TDF is supported by two factors. Firstly, there is a high genetic barrier to resistance via the TAM pathway or more likely through the K65R route. Secondly, it has been reported that there may be a fitness cost to the emergence of a viral strain with the K65R mutation conferring impaired transmission fitness. The population benefits of chemoprophylaxis will be increased if tenofovir resistant HIV has diminished fitness for transmission (Population Effects of Chemoprophylaxis, Travis Porco, Kimber Gross, Robert Grant, 2003). According to Dr Grant, chemoprophylaxis failure must therefore be seen as essentially very early treatment. Treatment with d4T or TDF within 72 hours of infection has been shown to lead to durably decreased levels of plasma viremia (Lifson 2000; Rosenwirth 2000)

Pharmacologic Issues in HIV Chemoprevention, Craig Hendrix, Director, Drug Development Unit, Johns Hopkins University

Craig Hendrix provided a comprehensive overview of the pharmacologic issues involved with HIV chemoprevention. From his extensive experience in microbicides development, Dr Hendrix noted that the fundamental questions outstanding are:

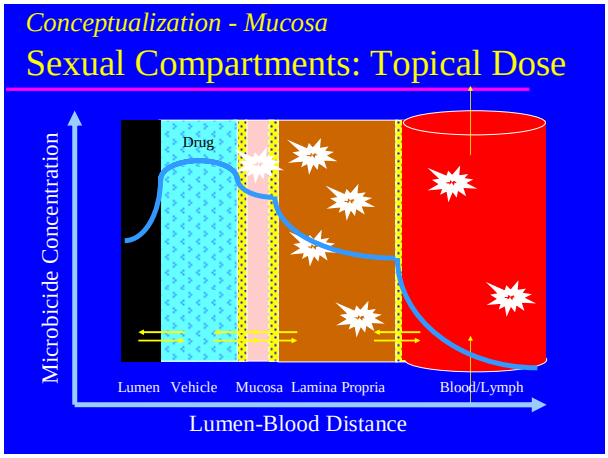
What is the right drug?
Does it affect prevention of shedding or prevention of infection and does it attack the virus, the cell or cell-cell and HIV interaction

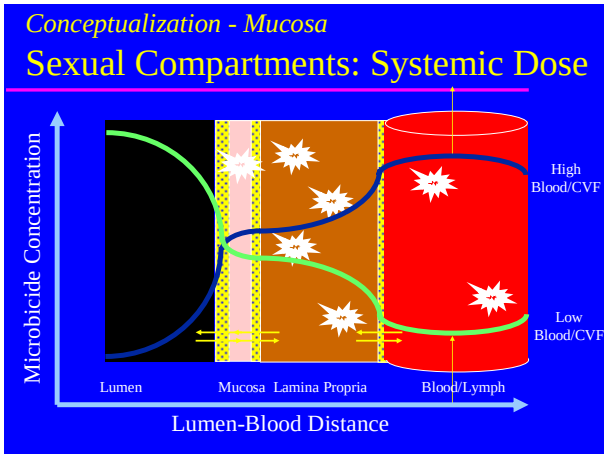
What is the right amount?
What is more important - peak concentration (Cmax), trough concentration (Cmin), exposure (area under the curve: AUC), inhibitory quotient (Cmin/IC50)

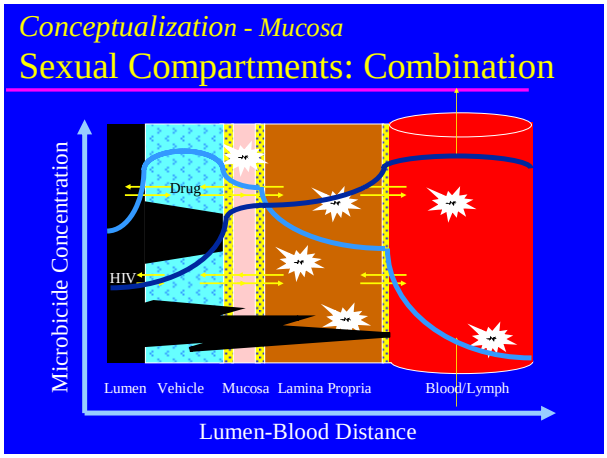
Where is the right place for delivery and action?
Distal-proximal (vagina-cervix; rectum-colon), lumen - mucosa - lamina propria – blood; HIV intracellular targets, cell-cell interaction

When is the right time?
Duration of virus (+/- cell) threat to susceptible cells? Duration of toxicity - recovery time, next exposure? Interval between dosing and exposure?

Human physiological characteristics especially the genital compartments in the case of local microbicides, determine the action and limitations of different drug profiles.







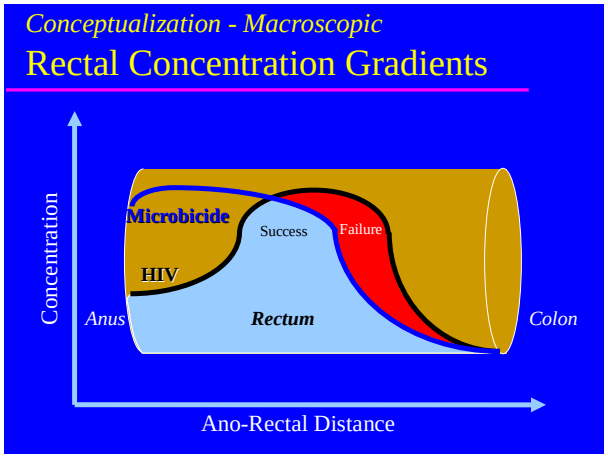
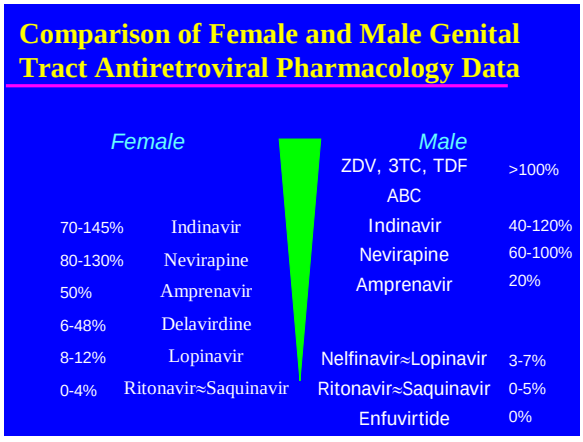
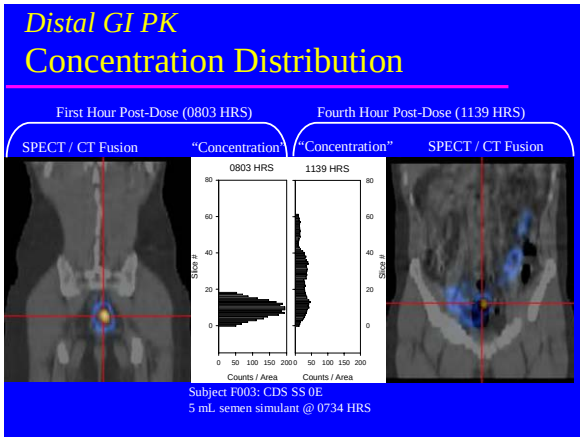


TABLE 1. Ratios (medians) and IQRs of the concentrations of indinavir, nelfinavir, lopinavir, and ritonavir in CSF, semen, and LN tissue compared to those in plasma

Sanctuary site	Concn ratio (IQR)[a]			
	IDV	NFV	LPV	RTV
CSF	0.17 (0.10–0.49)	0	0	0
Semen	1.9 (1.07–3.94)	0.08 (0.06–0.10)	0.07 (0.01–0.45)	0
LN tissue	2.07 (1.02–3.67)	0.58 (0.27–0.84)	0.21 (0.15–0.26)	0.64 (0–1.15)

[a] IDV, indinavir; NFV, nelfinavir; LPV, lopinavir; RTV, ritonavir.





Dr Hendrix outlined the pharmacologic considerations of PREP against key principles that will influence design of studies, pharmacokinetic action of potential compounds and measures of prophylactic efficacy.

Question 1: is there a preferred antiretroviral class or profile of agent based on PK profile?
Principle: outdistance and outlast the virus is the winning strategy

Question 2: does the site of action of a PREP compound impact on its efficacy, e.g., entry inhibitor versus intracellular reverse transcription or protease?
Principle: select mechanism of action relevant to site of action and target

Question 3: are there drugs that are better at penetrating genital compartments? Does this matter? How is it measured? How do drug levels in plasma or at sites of exposure impact on toxicity, especially if delivered locally?
Principle: efficacy (*adequate concentrations at site of action*) must be balanced against toxicity cognizant of adherence; toxicity, like efficacy, depends on access to site of action.

Question 4: topically-applied versus orally-administered treatment - which is better at preventing transmission?
Principle: efficacy must be balanced against toxicity cognizant of adherence

Question 5: how should studies be designed to answer pivotal PK, safety and efficacy questions?
Principle: learning (hypothesis generating) & confirming (hypothesis testing) cycles of investigation cooperate to increase fundamental knowledge in ways that inform therapeutics

Question 6: should we dose compounds differently based on its indication as treatment or prophylaxis? Is it easier to prevent transmission than to treat an established infection?
Principle: easier to prevent than treat – simple numbers game; efficacy balanced against toxicity in context of compliance

Question 7: is the risk of becoming infected with resistant virus higher with suboptimal exposures to ARVs?
Principle: risk of infection is related to amount of drug at site of transmission, but this likely a saturable relationship, and toxicity and adherence become counter-balancing burdens

Summary of discussion

Rob Dintruff from Abbott Laboratories outlined the challenges for industry in developing a PREP agent including the considerations that influence any investment in new treatment development. He defined those in terms of opportunity measured as risks and benefits, practical limitations and the rational sequence of drug development pathways.

Other industry members supported these concerns confirming that the specific challenges for them regarding investment in PREP would include the ambivalent and inconclusive data emerging from the TDF trials and the apparent absence of agreed parameters of what is to be achieved – prevention, attenuation of infection, limited transmission and the required levels of efficacy. David Reddy from Roche, Basel confirmed the need to develop effective animal models that would enable researchers to ask the most appropriate questions for PREP. He noted that ambiguous or negative data from prospective studies may in fact prove to be more damaging than helpful. Amy Keller from GlaxoSmithKline (GSK), USA confirmed that whilst there was interest in PREP amongst her colleagues, the question remained which of the drugs within their portfolio may be the most optimal to study for prophylactic use. This was further supported by Emilio Ledesma from Bristol Myers Squibb who felt that discussions such as these could help to define and concentrate the scientific questions, but also that companies could consider both licensed and more importantly, drugs in the development pipeline to assess the potential value of modelling emerging compounds as candidates for PREP.

Paul Stoffels from Tibotec, Belgium reminded participants that industry have technological and scientific expertise that they can and do contribute and stressed the immense need for collaboration between research agencies and industry. In an area where there is much speculation about the criteria for efficacy, Paul Coplan from the International Partnership for Microbicides added the need for systematic evaluation to inform which studies and sub-studies need to be practically supported, whilst Jean-Marc Steens from GSK, UK emphasised the need to learn from PMTCT models. Many of the industry members articulated their collective concern that whilst the economic incentive for PREP remained uncertain, there were in addition significant disincentives that constrained their enthusiasm for large-scale investment in PREP research, most notably the disruption to studies affected by some community activists in the field.

From a developing world perspective, John Idoko from Jos University Teaching Hospital in Nigeria outlined the major limitation of future PREP studies, confirming limited infrastructural capacity including both trained personnel and laboratory resources. He also noted that there were many outstanding concerns regarding the use of PREP, not least the ethical issues that had already been raised.

Given that HIV is most likely to be transmitted during acute infection, there were a number of concerns raised regarding the need to both identify and understand the biologic and virologic profile of acute infection and define the optimal time, infection stage and mode of intervention. Craig Hendrix raised the issue of whether it may be important to consider which drugs are preferentially phosphorylated within the cells and whether action before or after entry into cells may be of relevance. Bob Grant asserted the need to understand viral-specific enzymatic processes in order to develop optimal study and compound design adding that dendritic cells or other cells in the viral life cycle may have an impact on transmission. From a virologic perspective, Yasmin Halima from IAS asked whether HIV viral subtypes may impact on transmission, in particular subtypes C and E which have been reported to be more infectious. Also, whether HIV envelope characteristics may be of significance given that clade C for example is known to rarely evolve from NSI to SI phenotype (non-synctia and synctium-inducing correlated with early and late stage disease). Myron Cohen responded that this indeed may be of significance, but there was limited data on subtypes, envelope profiles and influence on sexual transmission. However, these viral differences should be carefully integrated and evaluated in future studies for their potential consequence on population transmission.

Interestingly, Myron Cohen also cautioned that the imperfect use of PREP, for example forgotten doses could mean that the subsequent restarting of PREP would actually serve as a PEP (post-exposure prophylaxis) regime. These issues have to be seriously considered by researchers and assessed for their implications for individual and public health. On the issue of whether making PREP or PEP available is likely to increase unsafe sexual behaviour, Bob Grant referred to data based on PEP following sexual exposure that did not associate biomedical intervention with behavioral disinhibition (Roland et al, JID)

The Chairs of the meeting, Joep Lange, Michel Kazatchkine and Pedro Cahn thanked the presenters and participants for their contribution to this informed and active debate. Yasmin confirmed that the next meeting of the IAS-ILF would be a satellite session at the IAS Rio Conference on Tuesday 26 July 2005.

Yasmin Halima, IAS-ILF Co-ordinator, March 2005

International AIDS Society, Ch. de l'Avanchet 33, PO Box 2, CH-1216 Cointrin, Geneva, Switzerland
Jacqueline van Tongeren, IAS-ILF Support Manager, T. +31 6 51 20 99 00 or +31 20 314 9300
Yasmin Halima, IAS-ILF Coordinator, T. +44 20 7729 7525 or +44 7973 726710