2nd Global Experts Summit: Leading by Example in the Public Health Approach to ART

SUMMARY REPORT

Vancouver, Canada
11-13 February 2009
CO-ORGANIZERS:

- The Global Fund
- World Bank

CO-HOSTS:

- British Columbia Centre for Excellence in HIV/AIDS
- Public Health Agency of Canada
- Agence de santé publique du Canada

INDUSTRY SPONSORS:

- Abbott
- Bristol-Myers Squibb Foundation
- Boehringer Ingelheim
- Gilead
- GlaxoSmithKline
- Merck
- Schering-Plough
- tibotec
2 Executive Summary

The International AIDS Society (IAS) convened a meeting in February 2009 to establish expert consensus on current international guidelines and further research needed to optimize the individual and societal benefits of the public health approach to ART. The 2nd Global Experts Summit: Leading by Example in the Public Health Approach to Antiretroviral Therapy (ART) was co-organized with the World Bank and Global Fund to Fight AIDS, Tuberculosis and Malaria and co-hosted by the BC Centre for Excellence in HIV/AIDS (BC-CfE) and the Public Health Agency of Canada (PHAC).

As the pace of ART programme scale-up in low and middle-income countries increases, a growing number of clinical, programmatic and health systems questions are emerging about how to deliver these programmes most effectively using the public health approach. The Vancouver Summit builds on the Sydney Declaration (2007), the World Health Organization (WHO) consultation on knowledge gaps in treatment and care (2008) and the WHO/IAS/Global Fund/World Bank Consensus Statement, released at the XVII International AIDS Conference (AIDS 2008), all of which raised awareness regarding the need for an operations research agenda.

The Vancouver Summit included a wide range of experts from multilateral organizations, the research community, civil society, donor agencies, the medical community and the pharmaceutical industry. The programme was divided into five thematic areas:

1. Maximizing the positive impact of ART on prevention
2. ART initiation
3. Optimization of ART drug regimens
4. Monitoring of ART
5. Programme implementation and health systems strengthening

Content experts delivered presentations within each of these areas, outlining current scientific and programmatic evidence, and identifying outstanding ART-related operations research questions. The presentations were followed by discussion and a summary of key discussion points by the session chair. Then, breakout groups organized by thematic area developed a series of recommendations for action. This was followed by a plenary discussion of the proposed recommendations.

Below are the consensus recommendations on (where relevant) international normative guidance and outstanding ART-related operations questions from the Vancouver Summit. They are intended to inform clinical management and advance a normative review and operations research agenda that will drive improvements in the development, delivery and evaluation of ART programmes using the public health approach.
2.1 Maximizing the Positive Impact of ART on Prevention

There was general consensus that ART guidelines should consider the added potential preventive impact of expanding ART coverage among those in medical need. This also should be considered when discussing the optimal time for the initiation of ARV therapy. The IAS-USA guidelines, for example, note that treatment should be considered at any CD4 count for individuals in sero-discordant couples.

**Operations Research Questions:**
- At what point does viral suppression (the ‘threshold effect’) translate into a preventive benefit?
- Does ART have an impact on other prevention measures, e.g. in the form of ‘risk compensation’?
- How can ART be delivered most effectively to optimize its preventive impact in addition to its impact on reducing morbidity and mortality in the individual?
- What monitoring strategies, systems evaluation, and health care delivery services are required to evaluate the impact of ART on prevention?
- Are efforts required to expand indications and access to ART to maximize its preventive potential?
- What is the quantitative preventive benefit of a given expansion of ARV coverage. Does this relationship vary with populations or transmission groups?

2.2 ART Initiation

**Normative Guidance Recommendations:**
- Normative agency guidelines need to be revised expeditiously, periodically and at a greater frequency than has been the case to date.
- ART should be initiated earlier, with strong evidence suggesting initiation be started at CD4+ cell count at or above 350/mm3.
- Regimens need to be well tolerated, safe, robust and convenient. Consistent with the recommendation for earlier ARV initiation, the role of nevirapine as first-line drug of choice should be revisited.
- Adherence support should be stressed, including travel support, food support and viral load monitoring.
- ART should be initiated in everyone with TB, irrespective of CD4+ cell count.
- ART should be offered to all HIV+ pregnant women.
- A critical review of data on the safety of efavirenz in pregnancy should be urgently conducted. The positioning of efavirenz as initial therapy among women of child-bearing potential may merit reevaluation accordingly.
Operations Research Questions:
Research should be preferentially conducted by local institutions under the auspices of national governments, with assistance from donors, multilateral institutions and academic institutions from high-income countries. Priority research questions related to ART initiation include:

- Identifying treatment outcomes, including time on first and second-line regimens, efficacy of regimens and patients lost to follow-up
- The effect of earlier ART initiation on transmission at a population level
- Pharmacovigilance (including long-term toxicity)
- Monitoring quality control of generic drugs
- Costing of earlier treatment initiation
- Drug resistance monitoring (both primary and secondary resistance)

2.3 Optimization of ART Drug Regimens

Normative Guidance Recommendations:

- Tolerability of treatment should be a key consideration in determining drug regimens
- Triomune should not be the global normative drug combination
- More optimal first line regimens should now be included, particularly boosted protease inhibitor (PI) based regimens. The role of novel drug classes should be considered in this setting.
- First line regimens should cover the whole range of CD4+ counts
- Raltegravir should be optimally used in second-line or salvage regimens with a boosted PI
- Multiple regimens and more options for clinicians should be part of normative agency guidance, such as newer boosted PI combinations.
- Atripla is to be recommended as a preferred initial therapy option. In this context, it is urgent to resolve whether efavirenz is safe for use during pregnancy.

For second and third-line regimens, in the absence of widely available genotyping, regimens including at least two new classes of antiretrovirals should be recommended to address potential issues of cross-resistance. Etravirine boosted by a PI should be considered for this purpose, as well as nucleoside-free regimens.

2.4 Monitoring of ART (CD4, Viral Load, Adherence, Resistance)

Normative Guidance Recommendations:

- Viral load monitoring should be included in normative agency guidance
- Need to develop cheaper and more accessible VL tests for better clinical monitoring
- Drug resistance testing at point-of-care and population level resistance surveillance should be used to help guide appropriate drug regimens
- Adherence monitoring should include data collection of early warning indicators (appointment keeping, drug pickup, pill-counting, etc.) to help guide clinical monitoring among ART programmes
Guidance on adherence monitoring should be included in overall clinical guidance

**Operations Research Questions:**
- How (and when) should viral load tests be used most effectively in resource-limited settings, including how to ensure sufficient quality assurance, timeliness and results verification as part of viral load testing standardization?
- Who is best placed to do deliver patient education programme it and what materials are required to support this programme?
- Are there better ways to use CD4 counts in conjunction with other mechanisms to monitor ART delivery more effectively?
- What is behind the discordance between clinical failure in patients with virologic suppression and vice versa?
- Point-of-care qualitative viral load testing technologies must be urgently developed.

**Stakeholder Actions/Roles:**
- Continuing medical education (CME) is required to ensure uptake of updated clinical guidance (including algorithms and clinical tools to guide ART monitoring)
- Patient education programmes should be included as a component of clinical monitoring for adherence.

2.5 Group V: Programme Implementation and Health Systems Strengthening

There were no normative agency guidance recommendations for this content area. Precursors to answering operations research questions on programme implementation and health systems strengthening are:
- Strengthening information systems capacity to monitor ART impact (including developing indicators, a minimum data set, data generation and standardized reporting systems and data use protocols)
- Establishing generic protocols to measure the impact of HIV management on the health care workforce, drug supply chain and other components of the health system

**Operations Research Questions:**
- What is the impact of HIV investments on health systems?
- How has the AIDS response in general and ART scale up in particular shaped or influenced broader national health policies, in terms of access to care, health financing, human resources and other health policies?
To address the need for the sustainability of ART programmes within a global financial crisis, research in this area must address:

- Evidence of results/achievements in the global response to AIDS
- Evidence of dangers if funding for HIV programmes is reduced or eliminated
- Benefits of building on existing successes (and available data) and scaling up

A multidisciplinary approach is required to answer these questions, and it is important that operations research be part of a strategic health information agenda.

3 Background and Global Context

The 2nd Global Experts Summit: Leading by Example in the Public Health Approach to Antiretroviral Therapy (ART),1 was held 11 – 13 February 2009 in Vancouver, Canada. The meeting was convened by the International AIDS Society (IAS), with the World Bank and Global Fund to Fight AIDS, Tuberculosis and Malaria as co-organizers and the BC Centre for Excellence in HIV/AIDS (BC-CfE) and the Public Health Agency of Canada (PHAC) acting as co-hosts. The goal of the summit was to establish expert consensus on the research needed to optimize the individual and societal benefits of the public health approach to ART among key stakeholders in the global response to HIV/AIDS. Specifically, the objectives of the summit were:

- To evaluate and build consensus on the most recent scientific data on ART with a focus on initiation, optimization, monitoring and delivery;
- To identify additional research required to identify how to maximize the preventive benefit of ART;
- To identify key actions needed to strengthen human and financial investment in capacity-building and implementation of a robust operations research agenda.

The summit objectives were designed to build on the success of the rapid scale-up of ART programmes in resource-limited settings over the past several years, which have increased the number of people on treatment from 400,000 in 2003 to 3 million by the end of 2007. The objectives are also predicated on ART programme delivery using the public health approach recommended by WHO, which includes standardizing drug regimens, simplifying formularies, simplifying clinical decision-making, standardizing treatment monitoring, standardizing management of toxicity and drug-drug interactions and monitoring HIV drug resistance at the population level.2 Implementing ART programmes using the public health approach also requires decentralized, integrated care delivery, task-shifting, free ART at the point of service delivery and strengthened procurement and supply.

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1 Hereinafter referred to as the Vancouver Summit.
While the public health approach has helped to rapidly expand access to ART in some of the poorest regions of the world, it has also raised clinical, programmatic and health systems questions regarding how to maximize the impact of these programmes.

The Sydney Declaration (released immediately prior to the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention in July 2007), called for 10% of all resources dedicated to HIV programming to be used for research towards optimizing interventions utilized and health outcomes achieved. The Declaration helped generate attention regarding the need to address programmatic and health systems delivery questions. In 2008, the WHO consultation with global experts on knowledge gaps in care and treatment, and the WHO/IAS/Global Fund/World Bank Consensus Statement, released at the XVII International AIDS Conference (AIDS 2008), built broader engagement and understanding of the urgent need to advocate for and invest in an operations research agenda to help strengthen delivery of HIV interventions. In addition to the stakeholders represented at the WHO consultation in 2008, the Vancouver Summit included representation from eight research based pharmaceutical companies: Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb Foundation, Gilead, GlaxoSmithKline, Merck, Schering-Plough and Tibotec.

This report summarizes the presentations, discussion highlights and recommendations for action. Final presentations and background materials from the summit, including a convenience sample summary of ART-related operations research, are available at [http://www.iasociety.org/Default.aspx?pageId=314](http://www.iasociety.org/Default.aspx?pageId=314).

Recommendations from the summit are intended to inform research and clinical guidance in this field, and will be the subject of a session at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009) in Cape Town, South Africa.

## 4 Summit Programme

The summit agenda was organized based on five thematic areas related to ART programme delivery in resource-limited settings:

1. Maximizing the positive impact of ART on prevention
2. ART initiation
3. Optimization of ART drug regimens
4. Monitoring of ART
5. Programme implementation and health systems strengthening

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The meeting was opened by the Hon. George Abbott, Minister of Health, Province of British Columbia, after which Julio Montaner, IAS President, welcomed participants and formally opened the meeting. Representatives from the IAS, The World Bank, Global Fund and WHO each provided brief introductory comments:

**International AIDS Society**
Craig McClure noted that although there has been significant discussion about operations research, there has been inadequate action undertaken since the 2007 Sydney Declaration. Scientific evidence has advanced significantly in some areas since then, and this meeting is an opportunity to review evidence, identify knowledge gaps, and recommend how to move forward on some key issues. He noted that the IAS was committed to continuing to engage industry and other stakeholders to advance operations research priorities.

**The World Bank**
Debrework Zewdie noted that the Bank was an early signatory to the Sydney Declaration and now has an established operations research agenda funded through its Global HIV/AIDS Program. The World Bank is in the process of incorporating research into all of its programmes and is working with its partners to support the development of a coherent international agenda on operations research. She noted that financial institutions are paying greater attention to operations research, but that much work remained to be done before it would be possible to reach the 10% goal identified in the Sydney Declaration. Barriers include:
1. The need for a transparent funding mechanism to support operations research and a consistent application process for countries
2. The lack of skilled human resources in resource-limited settings
3. Coordination between partners, particularly critical at the country level

She added that the impact of the current global financial crisis on HIV funding was unknown.

**The Global Fund to Fight AIDS, TB and Malaria**
Stefano Lazzari noted that primary bottlenecks in many countries remain the limited pool of skilled health care workers, poor infrastructure and limited support for proven interventions, adding that a health systems strengthening envelope is now a component of Global Fund grants. The Global Fund, which provides approximately ¼ of all HIV funding in low and middle-income countries, believes operations research has a strong role to play in effectively delivering HIV interventions; the overall budget for operations research as a

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4 The Sydney Declaration called on donors to allocate 10% of all resources for HIV programming to research (in addition to funds already committed to care, treatment and support).
component of Global Fund performance-based grants is around 5%, but growing.

**World Health Organization**

Yves Souteyrand reminded participants that ART coverage remains inadequate at just over 30% globally (based on current guidelines to treat at <200 CD4+ cells), that problems with health systems were resulting in early morbidity and mortality within ART programmes, and that the majority of people living with HIV are still unaware of their status. He briefly outlined the WHO priorities as defined in its strategy for research on health:

1. Advocate for operations research as an essential component of scale-up
2. Support capacity building at the country level to scale up operations research, especially human resources
3. Address gaps in information systems at country level to handle data
4. Translate research findings into action

He noted that WHO is currently finalizing generic tools for supporting OR development in priority topics (adherence to treatment; impact of treatment on prevention) as well as tools for better assessing treatment outcome and impact. He also noted that WHO will revise its ART guidelines this year and is organizing a consultation in early May on the feasibility of universal testing and treatment as a follow-up to the WHO’s recently published modelling study.\(^5\)

**5 The Role of the Pharmaceutical Industry**

**Chair:** Walter Strauss  
**Keynote Presentations:** Rob Dintruff and Patricia Doykos

The eight pharmaceutical companies participating in the summit collaborated on two presentations which reflect industry’s perspective on ART-related operations research.

R Dintruff (Abbott) presented on Current Strategies, Knowledge Gaps and Barriers in Delivering ART Programmes using the Public Health Approach. Key messages included:

- The need to plan for better but more expensive first-line regimens
- The need to consider that the switch rate (currently at 5%) to second-line regimens will accelerate
- To consider the implications for drug resistance and future treatment options
- The need to balance speed of ART roll out with quality of care and patient retention, with appropriate clinical monitoring (particularly viral load

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monitoring) supported by strengthened laboratory capacity and a greater emphasis on maximal viral suppression

- The need to address regulatory delays (e.g., through harmonization) as a barrier to treatment access and to ensure pharmacovigilance and bioequivalence monitoring are addressed


P Doykos (BMS Foundation) discussed opportunities for advancing the ART-related operations research agenda based on the principles of innovation and collaboration. Relevant industry core competencies were identified. These included pre-clinical studies and research/protocol development to planning for post-study issues such as publication planning and pharmacovigilance. A potential role for industry based philanthropy was also discussed.

A number of specific examples were identified, including:

- Working with Ministries of Health to help determine their research needs on key programmatic questions
- Leveraging the relationships established with key donors, government, multilateral agencies and civil society to advance an operations research agenda
- Providing technical advice on research planning, development, dissemination of research findings and integrating clinical research findings into programme delivery.


**Discussion Summary:**

Highlights of the discussion following the presentations included:

- Suggestions for industry to provide additional tools to promote adherence, which remains a significant issue in many ART programmes.
- The voluntary patent pool release should be seen as part of the solution to some of the regulatory issues identified by industry.
- Industry could make an important contribution by investing R&D in innovative, cheap, robust, reliable technologies to improve current diagnostic and monitoring tools; recent meetings between the Bill & Melinda Gates Foundation and industry are addressing this issue.
- The generic drug industry should be brought into these discussions at the next stage.

Participants suggested that industry collaboration should be driven by independent organizations, such as IAS, WHO, or UNAIDS.
It was also noted that several industry competencies (R&D, supply/distribution systems, drug regulation, etc) could be further leveraged. Of particular note were the outstanding R&D demands for diagnostics, new combination ARVs that would simplify dosing regimens, tools to support adherence, and the need for an integrated approach across industry regarding the public health approach to ART, which will also help deal with ART programme sustainability.

6 Session I: Maximizing the Positive Impact of ART on Prevention

Chair: Julio Montaner
Keynote Presentation: Reuben Granich

R Granich underscored that the focus of his presentation was ART as a prevention modality that addressed ‘community viral load’, not as an individual-based ART regimen used in post-exposure or pre-exposure prophylaxis. Key messages included:

- Despite significant investments and many trials of microbicides, vaccines and other biomedical interventions, only circumcision and STI treatment has been proven to reduce HIV transmission rates.
- Scientific evidence has confirmed that viral load is the single most important determinant of the risk of HIV transmission in any setting. It was therefore generally agreed that from a public health perspective reducing community viral load should be a primary target of the ART rollout.
- The recently published WHO modelling (Granich et al, Lancet 2008) study suggests that annual universal testing, immediately followed by ART for all who test positive (irrespective of CD4+ count or viral load) on a voluntary basis could eliminate HIV infection. This strategy would lead to marked reductions in morbidity, mortality and HIV incidence (an estimated 95% incidence reduction in 10 years), with resulting favourable cost-benefit impact.
- The feasibility challenges are substantial, but given the potential impact of this approach, WHO is hosting a consultation on this issue in May 2009 with key stakeholders to consider a range of issues, from bioethics to logistics.


Discussion Summary:

Participants made the following observations:

- The WHO modelling independently confirms the 2006 BC-CfE Lancet paper, regarding the case for expanding HAART coverage to decrease HIV transmission.
- Substantial funding, logistics and operational issues would need to be addressed, including whether the model should be revised for different sub-populations.
Respecting human rights will be critical if this approach is to be implemented.
The approach will require buy-in at the country level and among community-based organizations and NGOs.
A robust first-line drug regimen will be required to ensure optimal and durable viral suppression; existing issues regarding drug availability will need to be addressed.
Further research will be needed to understand whether this approach would be feasible. In particular, it is unclear whether healthy HIV infected individuals would be willing initiate ART in the absence of a clear medical indication.
The approach would need to address ‘prevention fatigue’, which was cited as a possible contributing factor in increasing HIV incidence among some populations in high-income countries.
Further modelling should include cost benefit analyses – particularly relevant given the current economic climate.

Key operations research questions include:
- At what point does viral suppression (the ‘threshold effect’) translate into a preventive benefit?
- Does ART have an impact on other prevention measures, e.g. in the form of ‘risk compensation’?
- How can ART be integrated in the combination prevention model?
- How can ART be delivered most effectively to optimize its preventive impact in addition to its impact on reducing morbidity and mortality in the individual?
- What monitoring strategies, systems evaluation, and health care delivery services are required to evaluate the impact of ART on prevention?
- Are efforts required to expand indications and access to ART to maximize its preventive potential?
- What is the quantitative preventive benefit of a given expansion of ARV coverage. Does this relationship vary with populations or transmission groups?
- How can the testing of the impact of ART on prevention be built into the ART roll out?
- Feasibility studies are needed to understand possible limitations of this approach.
- What is the potential impact of drug resistance and adherence on this approach?
- What are the complementary strategies needed to address sub-populations that may not be amenable to this approach?
Session II: ART Initiation

Chair: Papa Salif Sow
Keynote Presentation: Julio Montaner

J Montaner discussed new evidence regarding the optimal time to start ART, including new 2008 IAS-USA and US Department of Health and Human Services (DHHS) guidelines. In contrast to current WHO guidelines, the current recommendations include starting ART before CD4+ counts drop to below 350/mm³, and above 350/mm³ if there is evidence of high viral load, rapid CD4 decline, or co-morbidities (including chronic HCV or HBV infection, increased cardiovascular risk, underlying renal disease) that may be adversely affected by inflammatory events resulting from ongoing HIV replication. Current WHO guidelines recommend delaying ART initiation until CD4+ counts drop to below 200/mm³ partly due to earlier concerns regarding potential side effects which are less relevant in view of the improved safety profile of new generation drugs. Key messages included:

- Data from the SMART trial indicated most morbidity and mortality was related to non-AIDS defining illnesses.
- Disseminated inflammation occurs while HIV is unsuppressed, irrespective of CD4+ count (there is no asymptomatic phase of HIV), and is an important driver of non-AIDS morbidities, such as malignancies, and affects the heart, liver and kidneys.
- Deferring ART until patients have CD4+ counts of below 200 is associated with increased morbidity and mortality.
- 50% of people globally are starting ART below a CD4+ count of 200, including high-income countries
- All individuals will need treatment within 3 – 5 years of infection and treatment should thereafter be lifelong


Discussion Summary:
Several participants noted the inadequacy of current approaches to ensuring people receive counselling and testing. They stressed the need to better understand the psychosocial and economic issues involved in making the decision to get tested in order to increase testing uptake through both provider-initiated and voluntary testing modalities in a variety of settings. Other issues included structural barriers to both testing and treatment, such as financial disincentives where patients are sometimes billed for tests or part of treatment costs, need to be resolved in many low and middle-income countries.
Questions raised by participants related to the impact of recommending earlier ART initiation included:

- How can we ensure the delivery system can respond to increased demand?
- How can we ensure that people who need it receive appropriate, non-coercive HIV counselling and testing?
- How can we convince decision-makers of the need to increase resources to address the significantly expanded estimates of need that would result in earlier ART initiation?

8 Session III: Optimization of ART Drug Regimens

Chair: Darien Taylor
Keynote Presentation: Pedro Cahn

P Cahn proposed the following principles, with supportive data from a number of studies, aimed at optimizing ART drug regimens:

1. Start ART earlier and then determine how to resource the expanded response
2. Start safer: use first-line regimens that have good tolerability and efficacy
3. Provide second-line regimens in a timely fashion
4. Monitor treatment
5. Integrate ART programmes into the broader health system

P Cahn also emphasized the importance of addressing paediatric treatment issues, as children are often diagnosed late in HIV infection, have limited access to appropriate paediatric formulations and suffer high rates of morbidity and mortality as a result.


Discussion Summary

Participants noted that d4T should not be considered for either first or second-line treatment and suggested that viral subtype differences may have an impact on potential mutations and therefore clinical decisions. Other discussion highlights include:

- The need to incorporate pharmacovigilance (potentially as part of clinical guidance) in ART programme delivery
- Consider how to make resistance testing a more standard part of ART optimization in resource-limited settings
- Consensus on the need to start ART earlier in order to optimize treatment outcomes, to ensure regimens have the best side effect profiles and to educate physicians about switching to second-line regimens before mutations accumulate
- Better monitoring must involve refocusing on adherence and assessing the impact of regimens on sub-populations (e.g., pregnant women).
Session IV: Monitoring of ART
Chair: Mark Dybul
Keynote Presentation: Elly Katabira

E Katabira emphasized that intensified and improved ART monitoring is required to achieve optimal outcomes, underscoring the following issues for resource-limited settings:

- Counselling to address adherence and behaviour change
- Clinical evaluation should include assessing ART complications and new or worsening opportunistic infections
- Laboratory monitoring should include CD4+ count and viral load monitoring at least once per year
- Shortcomings of existing monitoring strategies include not accounting for variations in the health-seeking behaviour of patients, inadequate and expensive laboratory services and drug stock-outs.
- Clinical monitoring, adherence profiling and CD4+ testing should be used to prioritize viral load monitoring needs; operations research should be conducted to refine criteria regarding who should have a viral load test when resources are limited.


Discussion Summary
Participants agreed on the need for inexpensive point-of-care viral load and resistance testing technologies (such as a viral load dipstick test) that would also obviate the need for more expensive laboratory monitoring, although some cautioned that there was no clear scientific consensus on the value of viral load versus other monitoring strategies. Other discussion highlights included:

- A quantitative viral load assay is not necessarily required; basic technologies are currently available to determine whether viral load is above the limit of detection.
- Simplified algorithms to guide clinical decision-making regarding ART monitoring should be part of overall clinical guidance.
- A minimum data set for operations research should be established and collected across settings that would allow validation of particular monitoring strategies and technologies.
- UN agencies are working with pharmaceutical and diagnostic companies on developing POC technologies, including guidance on information security and use of unique IDs.

M Dybul noted that there was support for a Request For Proposal for point-of-care viral load and resistance assays and suggested reviewing existing databases to see if there is an immediate way of looking at viral load and resistance. Operations research questions include:
What approach to viral load assays will ensure switching occurs before resistance mutations accumulate?
What strategies are already being utilized to enhance adherence, and what is currently available in World Bank or PEPFAR evaluations that can contribute to clinical guidance?
How can we better collect and share data that will contribute to policy change?
Scale up issues: do processes that work on individual patients scale up to 1 million?

10 Session V: Programme Implementation/Health Systems Strengthening
Chair: Debrework Zewdie
Keynote Presentation: Jim Kim (via videoconference)

J Kim highlighted the need for HIV prevention and treatment to be integrated into primary care, citing a Haitian clinic as an example of how this could work. He emphasized the challenge of the ‘implementation bottleneck’ which may actually tighten if underlying issues affecting weak health systems are not addressed as part of the global response. He recommended an interdisciplinary approach to assess health system dynamics that include:
1. Business analysis at the clinic and system-level
2. Case studies
3. Simulation models
4. Hypothesis-driven research
5. Design delivery model
6. Implementation
7. Evaluation

He noted that – unlike in the clinical field – there is no normative framework for health system design; the HIV field needs to know how particular implementation strategies and programme designs lead to desired outcomes, positing a new ‘science of health care delivery’ that would address how best to deliver a health intervention to everyone.


Discussion Summary
Participants raised the following issues during the discussion:
- Multiple financing mechanisms have caused fragmentation; each NGO has its own capital infrastructure, staff, and other administrative supports.
- The Global Fund and PEPFAR will be critical partners in addressing health system delivery issues, given the size and scope of their investments.
Developing many shared methodologies is required to develop context-independent system designs that can inform implementation.

Non-health system bottlenecks also need to be addressed in operations research, especially for marginalized populations (e.g., the political will to implement proven interventions).

Establishing/strengthening the capacity of monitoring and evaluation units will be critical to informing health systems delivery approaches.

The HIV field must prove to donors that their investments can produce results quickly.

Operations research should be considered a key component of strategic health information (as part of ART programme monitoring and evaluation) required to strengthen and expand ART scale-up.

D Zewdie emphasized that the HIV field needs to be able to do a better job of establishing evidence of how disease-specific funding maximizes the benefits outside of targeted populations, raising a series of key questions:

- Can impact be demonstrated on reducing burden of disease?
- What is the role of government and donors in demonstrating outcomes?
- With respect to sustainability, how can we ensure long-term impact beyond the three or five year programmes and infrastructure?

11 Consensus Recommendations on Normative Guidance and ART-related Operations Research

Breakout groups were established to review the discussion and presentations, and to make recommendations within each of the five thematic areas, including identifying the potential role or actions of specific organizations. Recommendations from each breakout group are organized as follows:

- Normative agency guidance
- Priority operations research questions
- Stakeholder actions/potential roles

11.1 Maximizing the Positive Impact of ART on Prevention

Group I noted that the issue of changing clinical guidance and related indicators (such as CD4+ count) is separate from the issue of how to measure the impact of ART on prevention. Although there were no normative agency guidance recommendations from this group, it noted that the full impact of ART on transmission will not be realized without much broader uptake of HIV testing and intensified monitoring of policy changes on ART programmes.

Operations Research Questions:

- At what point does viral suppression (the ‘threshold effect’) translate into a preventive benefit?
- Does ART have an impact on other prevention measures, e.g. in the form of ‘risk compensation’?
- Where and how can ART be delivered most effectively as a prevention intervention?
- What monitoring strategies, systems evaluation, and health care delivery services are required to evaluate the impact of ART on prevention?
- Are efforts required to expand indications and access to ART as prevention?

The group suggested that there is a contradiction between short-term costs and long-term savings, between treating those with advanced HIV infection and those who are most infectious (i.e. during acute infection). Quantitative models, including cost-benefit analyses, are required on which to base decisions.

**Stakeholder Actions/ Roles:**
- Additional research funds to address ART as prevention may be available from PEPFAR (a request for applications will be issued shortly which includes this topic as a research priority)
- The NIH has an additional $10B for new research earmarked for disbursal before September 2009 and could be an important source of operations research funding.

### 11.2 ART Initiation

**Normative Guidance Recommendations:**
The ART initiation group made the following recommendations for updated normative agency guidance:
- Normative agency guidelines need to be revised expeditiously, periodically and at a greater frequency than has been the case to date.
- ART should be initiated earlier, with strong evidence suggesting initiation be started at CD4+ cell count ≥ 350.
- Regimens need to be well tolerated, safe, robust and convenient to take (noting that nevirapine should be avoided in patients with high CD4+ counts).
- Adherence support should be stressed, including travel support, food support and viral load monitoring.
- ART should be initiated in everyone with TB, irrespective of CD4+ cell count.
- ART should be offered to all HIV+ pregnant women.

**Operations Research Questions:**
Research should be preferentially conducted by local institutions under the auspices of national governments, with assistance from donors, multilateral institutions and academic institutions from high-income countries. Priority research questions related to ART initiation include:
- Identifying treatment outcomes, including time on first and second-line regimens, efficacy of regimens and patients lost to follow-up
- The effect of earlier ART initiation on transmission at a population level
- Pharmacovigilance (including long-term toxicity)
- Monitoring quality control of generic drugs
- Costing of earlier treatment initiation
- Drug resistance monitoring (both primary and secondary resistance)

**Stakeholder Actions/Roles:**
The group recommended that the pharmaceutical industry (including generic companies) provide adherence monitoring support/tools to ART programmes.

11.3 Optimization of ART Drug Regimens

**Normative Guidance Recommendations:**
The optimization of ART drug regimens group made the following recommendations for updated normative agency guidance:
- Tolerability of treatment should be a key consideration in determining drug regimens
- Triomune should not be the global normative drug combination
- More optimal first line regimens should now be included, particularly boosted protease inhibitor (PI) regimens and novel drug classes.
- First line regimens should cover the whole range of CD4+ counts
- Raltegravir should be optimally used in first or second-line regimens with a boosted PI
- Multiple regimens and more options for clinicians should be part of normative agency guidance, such as newer PI and boosted PI combinations.
- Atripla is recommended as the best combination compound, but the group noted that it was urgent to resolve whether it is safe for use in by pregnant women.

For second and third-line regimens, in the absence of widely available genotyping, the group noted that two new classes were available to address potential issues of cross-resistance and that Etravirine boosted by a PI should be considered for this purpose, as well as nucleoside-free regimens.

**Stakeholder Actions/Roles:**
The group recommended that resource limited settings be included as early clinical trial sites to help generate early clinical data and speed registration.
- Originator companies should consider voluntary licensing for new agents and consolidating expanded access programmes for patients exiting clinical trials or with second-line drug regimen failure.
- IAS should ask companies with new regimens to proactively allow voluntary licensing and to use the UNITAID patent pool.
- IAS should convene a meeting with regulatory authorities, in collaboration with WHO, to address the registrations process.
- IAS may also have a role in encouraging industry to increase clinical trial investments in the developing world and to expand their use of expanded access programmes.
11.4 Monitoring of ART (CD4, Viral Load, Adherence, Resistance)

**Normative Guidance Recommendations:**
The ART monitoring group made the following recommendations for updated normative agency guidance:
- Viral load monitoring should be included in normative agency guidance
- Need to develop cheaper and more accessible VL tests for better clinical monitoring
- Drug resistance testing at point-of-care and population level resistance surveillance should be used to help guide appropriate drug regimens
- Adherence monitoring should include data collection of early warning indicators (appointment keeping, drug pickup, pill-counting, etc.) to help guide clinical monitoring among ART programmes
- Guidance on adherence monitoring should be included in overall clinical guidance

**Operations Research Questions:**
- How (and when) should viral load tests be used most effectively in resource-limited settings, including how to ensure sufficient quality assurance, timeliness and results verification as part of viral load testing standardization?
- Who is best placed to do deliver patient education programme it and what materials are required to support this programme?
- Are there better ways to use CD4 counts in conjunction with other mechanisms to monitor ART delivery more effectively?
- What is behind the discordance between clinical failure in patients with virologic suppression and vice versa?

**Stakeholder Actions/Roles:**
The specific organizations responsible will vary depending on the local context, but following are additional recommendations on how to strengthen ART monitoring activities:
- Continuing medical education (CME) is required to ensure uptake of updated clinical guidance (including algorithms and clinical tools to guide ART monitoring)
- Patient education programmes should be included as a component of clinical monitoring for adherence.

11.5 Programme Implementation and Health Systems Strengthening

There were no normative guidance recommendations from this group, which noted that a precursor to answering the operations research questions it identified was:
- Strengthening information systems capacity to monitor ART impact (including indicators, a minimum data set, data generation and standardized reporting systems and data use protocols)
Establishing generic protocols to measure the impact of HIV management on the health care workforce, drug supply chain and other components of the health system

**Operations Research Questions:**
- What is the impact of HIV investments on health systems?
- How has the AIDS response in general and ART scale up in particular shaped or influenced broader national health policies, in terms of access to care, health financing, human resources and other health policies?

To address the need for the sustainability of ART programmes within a global financial crisis, the group recommended that research address:
- Evidence of results/achievements in the global response to AIDS
- Evidence of dangers if we stop funding HIV programmes
- Benefits of building on existing successes (and available data) and scaling up

The group emphasized a multidisciplinary approach to answering these questions, and the need for operations research to be part of a strategic health information agenda. An upcoming IAS-convened meeting on health system strengthening, funded by the Rockefeller Foundation, will provide additional opportunities to further develop the approach of the HIV field on this issue.