Wilton Park

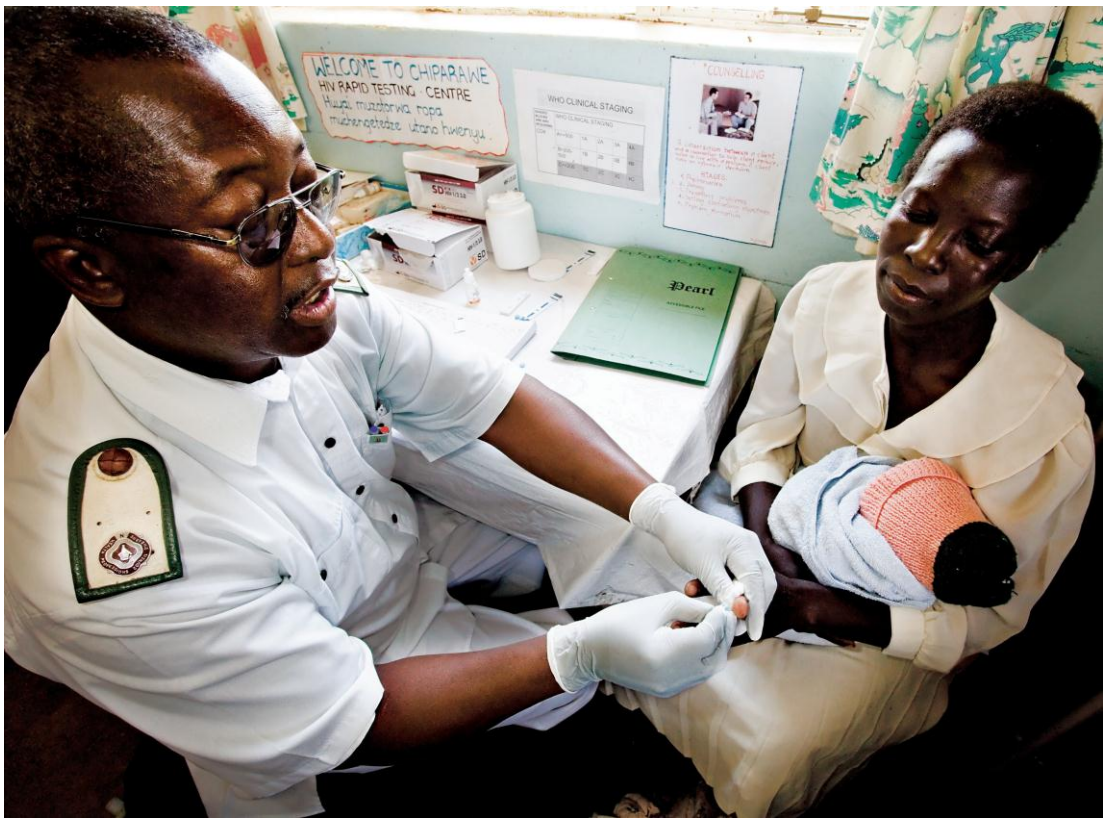

Image: James Pursey, courtesy of the Elizabeth Glaser Pediatric AIDS Foundation

Conference report

The new era in HIV/AIDS treatment and prevention: science, implementation and finance

Wednesday 27 – Thursday 28 June 2012 | WP1170

In association with:

UCSF GLOBAL HEALTH SCIENCES
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From evidence to action

GILEAD

Wilton Park

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Summary

This high level meeting was convened to discuss cutting edge scientific developments in HIV/AIDS treatment and prevention, and the implications for programme delivery and funding. Treatment as Prevention (TasP), a new approach to HIV/AIDS control, was the key topic of discussion. Early treatment of HIV-infected individuals, with anti-retroviral therapy (ART), saves lives and reduces HIV transmission from infected to non-infected persons. More specifically, a recent clinical trial (HPTN 052) demonstrated that early ART treatment of HIV-infected people reduced death and severe illness by 41%, and also achieved a 96% reduction in virus transmission[1]. This evidence raises the prospect of a strategic and large scale use of ART, in mass population 'test and treat' efforts, for clinical and prevention benefits.

Leading international experts participating in the discussion included: scientists; representatives of governments and national HIV /AIDS programmes; senior members of international development and technical agencies; and representatives of non-government organisations. The objective was to discuss the implications of these scientific findings, and consider 'cutting edge' - not 'business as usual' - solutions to ART delivery and scale up.

TasP raises complex cost benefit trade-offs for countries, funders, communities and affected individuals. Participations debated issues of programme acceptability and feasibility, including vitally important matters of treatment adherence, drug resistance and ethics, and implications for international and national funders in a widely resource constrained environment. However, the World Health Organisation (WHO) was urged to set TasP guidance based on the striking and growing scientific evidence versus being unduly influenced by feasibility, operational and financial challenges that will need addressing.[2 3 4 5]

There was an emerging consensus that TasP was a future public health measure of great importance in HIV/AIDS programming worldwide. Nonetheless, opinion diverged about the nature and pace of TasP introduction and scale up, given around half of all individuals currently eligible for ART are receiving treatment, with up to 40% loss to follow up (in some contexts) of people on ART, within the first year of treatment.

Some leaders called for 'bold action' arguing that undue caution, or delayed action may result in needless infection, and avoidable loss of life. Others argued for a more measured approach, one that pushed the same frontiers but in an incremental and 'safer' fashion by building on evidence gaps, adopting a network of 'demonstration sites' to learn from, and ensuring vigilant monitoring of 'red flags' or negative results or impacts. Ultimately, 'boldness' or 'caution' should not be viewed as dichotomous positions but a calibrated continuum of action guided by implementing context and conditions. The position many called for being ''how' and 'when' rather than 'if' to implement.

This paper summarises a lively and thoughtful debate by influential thinkers and practitioners in this field. Views on the scientific merit and substantial operational and financial challenges of a proposed rapid scale up of TasP were inextricably linked during discussions. For ease of reporting, they are examined and summarised separately below.

The science

1. According to a meta-analysis completed by WHO there are more than 50 on-going or planned research studies and trials on TasP. The details of three on-going community based studies of HIV test and treat in Southern Africa were singled out for description during the meeting (Annex 1).

2. Participants referred to compelling scientific evidence of the benefits of early ART treatment on mortality, morbidity and viral transmission in HIV infected individuals. Challenges to replicating these results in population - based HIV test and treat interventions, especially within the context of weak and poorly functioning health systems, were readily recognised and debated at length (see below).

3. What constitutes an adequate level of evidence for widespread TasP introduction was explained in detail. Some participants argued that there was currently adequate evidence to justify moving forward with TasP roll-out and implementation. Research and practice was viewed as symbiotic at this stage of the knowledge cycle. 'Waiting for more results' before taking decisive action was considered a mistake. For to do so, arguably, risks more lives and impedes stronger HIV control. Other experts questioned the risks of taking premature action and favoured step wise, carefully controlled TasP scale up. A "dash to action" could magnify levels of poor treatment adherence, with ramifications on drug resistance. Finding a balance among scientific evidence, implementation realities and acceptability was the crux of the debate.

4. It was highlighted that within a year, current large population based trials, undertaken within the context of routine service delivery (e.g. PopART in Zambia), will yield crucial data on TasP feasibility, in terms of coverage, uptake and cost.

5. The reflections of the eminent epidemiologist Sir Austin Bradford Hill[6] were quoted by one participant during these discussions:

> "All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.
>
> Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on 8:30 the next day." [page 300]

Some facts

6. The case for a rapid scale up of TasP was supported by a range of evidence and facts. Illustrative examples were:

   - **Burden of disease:** 34 million people are currently living with HIV, with 2.7 billion new infections each year.
   - **Test and treat benefits:** Ecological and surveillance studies from North America, Botswana, South America, Brazil and Malawi have shown associations with increased HIV testing and ART coverage and HIV and /or tuberculosis reductions.
   - **Scaling up of treatment can be achieved and achieved rapidly:** For instance, the number of people receiving ART increased from 50,000 to around 6.6 million within ten years, the majority in sub-Saharan Africa (with comparatively weaker health systems).
   - **Prevention remains a formidable challenge and TasP has the potential for large impact:** There are around 2.7 million infections per year, with only 20-30% of people aware of their HIV status, and other effective prevention measures, for example male circumcision, achieving low levels of take up and scale-up. Yet evidence supportive of effective TasP introduction suggests that:

- **ART demand and uptake** occurs in the context of good information, counselling and free ART[7].
- **Compliance:** High rates of compliance are possible and with higher levels than that achieved in developed countries.[8 9 10]
- **Drug resistance:** Good treatment with high levels of coverage and compliance will reduce and manage drug resistance.[11 12 13 14 15 16]
- **Behaviour change:** People who know their status (or are on ART) are less likely to engage in risky sexual behaviour.[17 18 19 20]
- **Treatment side effects:** Medication tolerability has improved significantly and people who cannot tolerate a particular regimen often have the option to switch to others.

- **Frontloading costs for wider benefit:** ART is cost effective and whilst early treatment will require frontloading investments, there will be overall gain in terms of patient and societal impact, including infection control.[21]

Knowledge gaps

7. Gaps in knowledge were acknowledged. Examples cited included:
   - **How** can TasP be optimally implemented?
     - For testing whole populations?
     - For effectively linking people diagnosed with HIV people to care?
     - What are TasP implications for already overstretched health systems, for example procurement and supply chain systems, laboratories and human resource management?
   - **Uptake:** Is it possible to achieve levels of treatment uptake that will provide an effect at population level? If so, what are those levels?
   - **Adherence:** How do we improve treatment adherence in order to avoid wide scale resistance? What do we know about the behaviour and treatment adherence of people living with HIV who feel healthy over time?
   - **Testing models:** What are the best models for HIV testing outside the health facility such as community and self-testing?
   - **Intervention packages:** What are optimal intervention packages and strategies to best reach or engage key populations, such as men who have sex with men, sex workers, and injecting drug users?
   - **ART eligibility thresholds:** On-going randomised clinical trials (RCTs) are examining the clinical benefits of different eligibility thresholds for when to initiate ART.
   - **Consequences of long term ART:** What are the consequences of long term ART to the infected individual? Could possible negative effects outweigh positive effects of early treatment?

Balancing evidence for policy and action

8. Current WHO guidance recommends TasP for serodiscordant couples, the population studied in the HPTN 052 trial. Updated WHO guidelines, including programme recommendations, are expected to be issued in 2013. Discussants made points that the framing of this guidance:
   - should have universal applicability (not one recommendation for richer countries and another for poor countries);
   - should not be ‘lowest common denominator’ guidance constrained by operational,

financial and political realities versus the primary strength of the scientific evidence.

9. Balancing the needs of individuals with that of population benefit was raised as an ethical consideration. For some, a tension between individual versus population benefit was identified. For instance, early ART treatment for a young person has trade-offs with possible increased risks of cancer or coronary events and other health issues. Moreover, the long term consequences of ART (50 years plus) are unknown. For others, this tension was not valid. In their view, individuals should not be coerced into treatment and treatment toxicity was considered minimal.

10. The importance of ongoing study results was underlined but not at the expense of delaying action. For many participants, the current evidence base is sufficient for moving forward with policy and action. Others stressed that such action be undertaken in contexts where limits can be pushed safely and results carefully monitored (i.e. vital when moving from trial conditions to population based implementation delivered via routine health services).

Implementation considerations

11. There is modest global ART coverage of people in need. Global coverage is estimated to be about 50% of those currently eligible for ART under WHO guidelines, with approximately a third of all people with HIV knowing their status. Even in countries with high testing rates (for example the United States of America), the proportion of HIV infected individuals that become virologically suppressed is quite low (i.e. a marker of programme effectiveness). Whilst recognising TasP as a breakthrough for disease control, some participants favoured prioritising and targeting effort. Given the modest coverage of people with a CD4 count of 350 or less (the threshold set in current WHO guidelines), more effective tackling of this challenge was warranted before initiating more ambitious ventures.

12. Challenges to TasP effectiveness are similar to factors influencing ART scale up – namely, adherence, retention, controlling drug resistance, health system capacity, equity of access and addressing stigma and discrimination. A range of demand and supply side challenges were raised in discussion, including:

    - **Demand creation:** This was not considered the biggest challenge. This has been demonstrated as feasible, and evidence of reaching and testing 80-90% of a population in Zambia was cited.
    - **Country health systems:** A number of limiting factors were highlighted. (i) Laboratory capacity in many countries was deemed inadequate for current needs, let alone responding to increased demands. (ii) Insufficient human resources for health were identified as another concern. The need for task shifting was identified, yet professional resistance (particularly from doctors, including Ministers of Health) was anticipated. (iii) Patient confidentiality may be compromised with larger numbers of staff involved in care delivery. (iii) Supply chain weakness and drug stock outs were cited as key challenges to fully implementing and sustaining TasP.
    - **Treatment thresholds:** Currently recommended treatment thresholds were deemed limiting by some commentators. A ‘treat on presentation’ strategy (i.e. not constrained by CD4 count levels) was favoured by many.
    - **Innovation and simplification:** Innovation and treatment simplification were considered important to programme effectiveness. Point of care testing, home testing and simplification of treatment regimes were all mentioned.
    - **Donor co-ordination and service integration:** The continued need for effective donor co-ordination was underlined, as was the need for an emphasis on disease integration and chronic disease management within weak systems.
    - **Migrant workers:** Migrant labour lifestyles were identified as a neglected epidemic driver that requires greater attention. TasP provides a breakthrough in disease control measures but other epidemic drivers should not be neglected.

Country views and experiences

13. Country views on TasP and current treatment realities were shared during the meeting by a number of senior country representatives. Views and readiness for TasP differed by country and were mediated by the nature of the epidemic and local context. A flavour of the points made is summarised in Box 1.

Box 1: TasP – country views and experience

Rwanda

- TasP is considered a timely prospect in the context of HIV control in Rwanda.
- Rwanda is approaching a situation where the number of new infections may be lower than those dying from infection. This transition has happened elsewhere (for example in Thailand and Cambodia) but would rank amongst the first in Africa. Strong treatment services were reported to be widely available and national efforts were directed at aiming for zero new infections.

Thailand

- Thailand was also deemed ready for TasP. Every Thai citizen is entitled to two free HIV tests per year, and there are currently around 250,000 patients on ART.
- Research on test and treat is currently in progress, and feasibility and acceptability has been demonstrated in key groups such as men who have sex with men (MSM). Health care provision is strong and domestically funded.
- Challenges flagged were:
  - (a) *How* to scale up nationally?
  - (b) *How* to finance STD screening (a complementary strategy)?
- Experts pointed out that concentrated HIV epidemics, such as occur in Thailand and Vietnam, have different test and treat requirements compared with generalised epidemics which will require strategic consideration.

Nigeria

- The need for stronger political 'buy in' from local government leaders for resource mobilisation and effective programme delivery was identified as key in the context of Nigeria's decentralised health care system.
- Resistance from medical practitioners to proposed task shifting was predicted.
- Stronger efforts to tackle corruption was identified as key to effective resource allocation and use.

South Africa

- Health services are operating under tremendous strain, with high ranking officials acknowledging that health services in 8 out of 9 of the provinces are already 'on their knees' with no elasticity to absorb any increased service demand generated by TasP.
- A testing campaign targeted at men who have sex with men and sex workers was launched in July 2012. By 2016, it is hoped that 80% of these populations will be screened (a target in the national plan). Monitoring any population level impact from this will be important.
- Concerns about drug resistance in relation to the current treatment regimen were stressed and have major implications for any test and treat strategy.
- The need to go beyond TasP by tackling underlying causes of poverty for HIV prevention was articulated. For example, it was stated that around 20% of new infections occur in young women who have no access to cash. Reference was made to three recent studies that demonstrated cash grants provided to young women resulted in reductions in new infections. Such interventions are the subject of debate and trade-offs need to be weighed.

Jamaica

Challenges to the successful introduction of TasP in Jamaica were identified. These included some specific concerns about children and adolescents.

Broad challenges included:

- Leadership inertia - there is a national policy to undertake HIV testing in all hospital admissions and Accident and Emergency patients. The policy has been in place for six years, however, to date, it has not been carried out in any hospital;
- Laboratories are weak and resist rapid testing in the field;
- There is poor integration of HIV treatment into general medicine;
- There is currently sub-optimal ease of treatment access. Patients may have distances to travel, followed by long waits at treatment facilities;
- The reliability of ART supplies could be better – stock outs occur;
- Population based ART programmes would require more financial resources. However, if there were political will and commitment this was not considered the biggest hurdle.

Concerns voiced about children and adolescents were:

- There are currently about 980 children on treatment. Most acquired HIV from mother to child transmission. The majority are on ART, including 15% on second line drugs. These children are growing up and becoming sexually active;
- There is a need for age appropriate disclosure to/from the child. Children younger than 18 years of age require parental consent for testing;
- Adolescence is a time for rebellion and experimentation. Treatment adherence in this group is particularly challenging;
- There are disparities in access to diagnosis, treatment and care services for children. Only approximately 23% of children (15 years or younger) have access to ART in low or middle income countries versus around 51% of adults;
- Paediatric ART optimisation is required for example availability and palatable

Financial implications

14. The financial costs and affordability analysis of population-based ART programmes, such as TasP, currently rests on modelling predictions given programmes have yet to be implemented in high prevalence countries. The findings of a background paper[22] prepared for this meeting were presented. This work modelled the prevention benefits and costs of an expanded HIV treatment programme in South Africa, at different levels of ART expansion. Conclusions were:

    - **Results so far:** To date, treatment efforts appear to have reduced new infections by 15-30% in South Africa over the past six years;
    - **Implications of new ART guidelines:** Implementing an expanded ART programme consistent with South Africa's recently updated eligibility guidelines is predicted to lower the number of new infections by an average of 43,000 per year, over the coming decade, compared to the older treatment programme which had a lower treatment eligibility threshold, and consequently treated smaller numbers of infected individuals at lower CD4 counts. This expanded ART program was judged to be affordable for South Africa, assuming that the economy continues to grow and the government maintains its current rate of increase in health and AIDS spending;
    - **Implications of universal test and treat:** A more ambitious approach based on universal test and treat would further reduce the number of new infections in South

Africa. However, it is unclear that such an aggressive programme would succeed in driving new infections close to zero, thus virtually ending the epidemic. The affordability of a universal test and treat approach was judged to be questionable, when its projected costs are compared with the expected growth in government and donor expenditures;

- **Implications of a multi-pronged prevention programme:** A multi-pronged prevention approach that combines expanded treatment with other proven cost-effective interventions, such as male circumcision, plus potentially effective new methods like pre-exposure prophylaxis, was judged to have a better chance of more sizeable reductions on new HIV infections, than a focused reliance on a dramatically expanded test and treat strategy.

15. Table 1 compares projected costs in 2015 for each of these scenarios. This compares to a 2011 position of ART costs of ZAR 7.8 billion (US$ 0.93 billion), which constitutes 63% of total national AIDS spending, and about 8% of the government health budget.

Table 1: 2015 projected TasP costs in South Africa by scenario

	Current Practice	Expanded Effort	Universal Test & Treat
Cost of ART ZAR billion (USD billion)	R 11.3 (US$ 1.35)	R 16 (US$ 1.92)	R 26.1 (US$ 3.13)
Share of estimated AIDS spending	38%	54%	88%
Share of estimated health budget	7%	10%	17%

Scenario definitions are:

- **Current Practice:** Individuals can access ART after symptoms show, CD4 < 350 cells/mm3 from 2011, 15% drop out in first year;
- **Expanded Effort:** Individuals are tested every two years; ART is initiated with a CD4 ~ 350; effective linkage to care, 4% drop-out rate; and;
- **Universal Test and Treat:** 90% of people receive an AIDS test every year, ART is initiated immediately after testing positive, 2% drop-out rate.

16. Others made the case that ART is affordable in all but 11 countries in southern and East Africa. A major donor to HIV programmes in the region was skeptical of this analysis. Others argued the issue was not one of country affordability but often lack of country prioritisation and corruption. The refrain that 'game changing' possibilities should not be limited by lack of ambition was echoed. A reluctance to recommend wide-scale TasP based on financial constraints alone was to be avoided. Instead, internationally endorsed treatment recommendations can galvanise and mobilise financing.

17. Financial viability is anticipated as being based on several solutions rather than one:

- **Strategic investment:** The need and opportunity for programme investment, including re-programming of funds, in high impact interventions was underlined. For example, the Global Fund to Fight HIV, Tuberculosis and Malaria (GF) is currently funding 225 HIV/AIDS grants over 121 countries. As of June 2012, the portfolio of GF total approved HIV grants was approximately 8.2 billion USD of which 6.6 billion USD is committed and 4.6 billion USD disbursed. In the next two years it is calculated that 7-8 billion USD will be available for re-programming as Phase 2 grant renewals are appraised. Grant reprogramming provides a strategic opportunity to ensure investment in high impact interventions.

- For example, 14 countries were reported to have participated in GF re-programming by the end of 2011. Consequently, 83.7 million USD was re-programmed and made available to prevention of mother to child transmission programmes.
- The efficacy and return on investment of some current programme investments were questioned. For instance, behaviour change communication programmes accounted for over 45% of Global Fund prevention spend up to 2009.

- **Counterpart funding:** The importance of and need for recipient country counterpart funding for HIV programmes was agreed. It was noted that of the 53 countries which signed the Abuja Declaration in 2001 only about six have reached the target of allocating 15% of budget spend to health. It was also noted that 88% of funding for HIV/AIDS work in Africa is from international sources (primarily the Global Fund and The United States President's Emergency Plan for AIDS Relief (PEPFAR). This observation underlines a serious vulnerability in countries and programme sustainability. Increased domestic resource allocation for work in HIV/AIDS was considered as critical, whether from general taxation, or social health insurance, or special levies and taxes.
- **Public private partnerships:** Wider and more inclusive partnerships arrangements are conducive to expanding financing and co-operation options.
- **Market leveraging:** Better value for money can be achieved through optimising purchasing power and market position. For example, 37% of GF resources are spent on commodities and health products, including ART. This creates significant purchasing power and the opportunity for market leveraging to generate price reductions.

Summing up

18. In summary, discussions at this meeting were based on the interplay between boldness and caution. There was clear agreement about the huge potential beneficial impacts of TasP on HIV prevention and control and a general consensus that TasP was a clear 'direction of travel' for HIV /AIDS programme strategy and implementation.
19. Expert opinion differed about the speed and nature of TasP introduction and scale up. Some experts argued for a more measured pace to introduction based on stronger evidence about 'how' to effectively scale up versus a rush to action. Other experts strongly argued that delayed action will cost lives. In their view, current evidence justifies moving forward whilst recognising there remain significant gaps in evidence, with important issues still to be clarified.
20. Importantly, the counterfactual case cannot be ignored. Despite impressive increases in the number of people on antiretroviral therapy, the number of new infections each year is roughly double the number of people newly placed on antiretroviral therapy. This implies a losing battle based on a model of 'business as usual.' The upfront cost of bold and assertive scale-up may be large, but the cost of 'continuing as we are at the moment' is expected to be far larger.
21. Country readiness for action varies. Large demonstration projects will be the most powerful advocacy tools for others to follow suit. This will be especially the case if the large demonstration projects are accompanied by rigorous measurement and evaluation. This measurement and evaluation is clearly a global public good and should be paid for by international sources. Demonstration projects could involve the whole population of a small country, such as Botswana, Lesotho or Namibia. This could focus on a defined part of a larger country, such as Kwazulu-Natal in South Africa, or a defined population such as the workforce and their families of the Anglo-American Corporation.
22. Large expenditures now, will lead to cost savings in the medium term it is argued. However, that does not fully address the problem of affordability, which is also a cash-flow problem.

Affordability can be potentially addressed both by making the task cheaper and by mobilising additional sources of funding. Concerning making the task cheaper, technologies and delivery mechanisms can be simplified. Considerable progress has already been made on these fronts. Concerning new sources of funding, the most immediately available option is reallocation within the Global Fund and PEPFAR budgets. Much Global Fund and PEPFAR money is spent on things other than testing and treatment. The impact of these non-test and treat investments is sometimes modest and sometimes unknown. It is suggested that there is a strong case for considering substantial reallocation of existing resources towards testing and treatment. Other possibilities for financing also exist, including incorporating HIV treatment cover into national social health insurance systems, particularly in countries with moderate or low HIV prevalence rates. New sources can also be seriously considered.

23. Key features of this bold agenda are summarised (Box 2).

Box 2: The 'bold agenda

- **The need for bold action**, based on the new drugs, highly successful access programmes, clinical evidence in favour of starting treatment early, and significant prevention gains that would follow from greatly scaling up the number of people on treatment.
- **Leadership and clear guidance around universal testing and treatment:** WHO and UNAIDS have a particularly important role to play here.
- **Use the best drugs with the lowest lifetime cost:** Not necessarily the cheapest drugs. This also means that countries are encouraged to adopt the most up-to-date and best practice treatment guidelines.
- **A single pill per day:** unless there is a really good reason to do otherwise, as treatment simplification for patients creates the opportunity for greater treatment adherence and a lower risk of the development of drug resistance.
- **Learn by doing at scale.** Learning about massive scale-up will not come from modelling or speculating about it. 'Learning by doing' at large scale is recommended and ensuring vigilance using robust monitoring and evaluation. Demonstration sites need to be carefully selected based on a calculated appraisal of country readiness. This will lead to on-going improvements in policy and implementation.

Dr Martine Donoghue
HLSP Institute August 2012

References

[1] Cohen MS, Chen YQ, McCauley TG, Hosseinipour MC et al for the HIV Prevention Trials Network (HPTN) 052 Study Team. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med; published on July 18, 2011, at NEJM.org.

[2] Sheton J. ARVs as HIV Prevention: A Tough Road to Wide Impact, Science. 2011; 334: 1645-1646.

[3] Mayer KH, Krakower D. Antiretroviral Medication and HIV Prevention: New Steps Forward and New Questions. Ann Intern Med. 2012; 156: 312-314.

[4] Garnett GP, Becker S, Bertozzi S. Treatment as Prevention: Translating Efficacy Trial Results to Population Effectiveness. Curr Opin HIV AIDS. 2012; 7: 157-163.

[5] Barnighausen T, Tanser F, Dabis F, M-L Newell. Interventions to Improve the Performance of HIV Health Systems for Trial-as-Prevention in sub-Saharan Africa: The Experimental Evidence. Curr Opin HIV AIDS. 2012; 7: 140-150.

[6] Bradford Hill A. The Environment and Disease: Association or Causation. Proceedings of the Royal Society of Medicine. 1965; 58; 295-300.

[7] Granich R, Muraguri N, Doyen A, Garg N, Williams BG. Achieving Universal Access for Human Immunodeficiency Virus and Tuberculosis: Potential Prevention Impact of an Integrated Multi-Disease Prevention Campaign in Kenya. AIDS Res Treat. 2012; 2012: 8.

[8] Lima VD, Harrigan R, Bangsberg DR, Hogg RS, Gross R, Yip B, et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J Acquir Immune Defic Syndr Hum Retrovirol. 2009; 50: 529-36.

[9] Lio MMS, Carbini R, Germano P, Guidotti G, Mancinelli S, Magid NA, et al. Evaluating Adherence to Highly Active Antiretroviral Therapy with Use of Pill Counts and Viral Load Measurement in the Drug Resources Enhancement against AIDS and Malnutrition Program in Mozambique. Clin Infect Dis. 2008; 46: 1609-16.

[10] Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. J Am Med Assoc. 2006; 296: 679-90.

[11] Dunn D. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. Br Med J. 2005; 331: 1368-

[12] Chaix ML, Descamps D, Wirden M, Bocket L, Delaugerre C, Tamalet C, et al. Stable frequency of HIV-1 transmitted drug resistance in patients at the time of primary infection over 1996-2006 in France. AIDS. 2009; 23: 717-24.

[13] Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2010; 10: 155-66

[14] Tam LW, Chui CK, Brumme CJ, Bangsberg DR, Montaner JS, Hogg RS, et al. The relationship between resistance and adherence in drug-naive individuals initiating HAART is specific to individual drug classes. J Acquir Immune Defic Syndr Hum Retrovirol. 2008; 49: 266-71.

[15] Gill VS, Lima VD, Zhang W, Wynhoven B, Yip B, Hogg RS, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. Clin Infect Dis. 2010; 50: 98-105.

[16] Uy J, Armon C, Buchacz K, Wood K, Brooks JT. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. J Acquir Immune Defic Syndr Hum Retrovirol. 2009; 51: 450-3.

[17] Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. AIDS. 2006; 20: 85-92

[18] Bechange S, Bunnell R, Awor A, Moore D, King R, Mermin J, et al. Two-year follow-up of sexual behavior among HIV-uninfected household members of adults taking antiretroviral therapy in Uganda: no evidence of disinhibition. AIDS Behav. 2010; 14: 816-23.

[19] Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. J Am Med Assoc. 2004; 292: 224-36.

[20] Venkatesh KK, de Bruyn G, Lurie MN, Mohapi L, Pronyk P, Moshabela M, et al. Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics. AIDS. 2010.

[21] Venetelou B, Arrighi Y, Lamontagne E, Carrieri P, J-P Moatti. The Macroeconomic Consequences of Renouncing to Universal Access to Antiretroviral Treatment for HIV in Africa: A Micro-Simulation Model. PLoS ONE. 2012; 7(4); e34101. www.plosone.org

[22] Hecht R, Eaton JW, Kuemmerle P, Partridge G et al. The Prevention Benefits of Expanding AIDS Treatment: How Large and How Affordable Are They? Unpublished.

ANNEX 1: Details of Three Community Based Test and Treat Trials Currently Underway in Southern Africa

Study	Location	Research communities	Intervention	Control	Primary Outcome	Estimated impact on incidence & power
PopART (HPTN 071)	Zambia & South Africa (Western Cape)	21 communities (7 matched triplets). Total population 1.2m	Intervention Arm A: • Universal voluntary testing + intensive linkage to care • Combination prevention for HIV negative individuals including medical male circumcision • ART for HIV positive individuals irrespective of CD4 count Intervention Arm B: • Universal voluntary testing + intensive linkage to care • Combination prevention for HIV –ve care including MMC • ART for all HIV positive individuals based on national guidelines for eligibility	Control Arm C: Enhanced standard of care	HIV incidence at 2 years Measured in a cohort of 52,500	50-60% (Arm A) or 25-30% (Arm B) reduction compared to Arm C >95% power (A vs C) 71-95% power (A vs B)
TasP	South Africa (KwaZulu Natal)	34 communities planned (currently funding for 4). Total population approx. 85,000	• Extensive counselling and testing • Comprehensive prevention programme • ART for HIV positive individuals irrespective of CD4 count	Control Arm: Same but with ART according to WHO guidelines	HIV incidence at 2 years Measured in cohort of 42,500	30% reduction with 90% power
Botswana CP Trial	Botswana	30 villages (15 matched pairs). Total population approx. 180,000	• ART for viral load ≥10,000 (at any CD4) + standard of care + package of increased testing, medical male circumcision and prevention of mother to child transmission • Efforts to increase retention in care	Control Arm: Standard of care	HIV Incidence at 4 years Measured in a cohort of 15,000	50% reduction with 99% power