Published in final edited form as:
Curr Opin HIV AIDS. 2010 July ; 5(4): 298–304. doi:10.1097/COH.0b013e32833a6c32.

Highly active antiretroviral treatment as prevention of HIV transmission: Review of scientific evidence and update

Reuben Granich[1], **Siobhan Crowley**[1], **Marco Vitoria**[1], **Caoimhe Smyth**[1], **James G. Kahn**[2], **Rod Bennett**[3], **Ying-Ru Lo**[1], **Yves Souteyrand**[1], and **Brian Williams**[4]

[1]Department of HIV/AIDS, World Health Organization, Geneva, Switzerland [2]University of California at San Francisco, San Francisco, United States [3]Independent Consultant, United Kingdom [4]South African Centre for Epidemiological Modelling and Analysis, Stellenbosch, South Africa

Abstract

Purpose of review: describe why this review is timely and relevant—An estimated 33 million people are living with Human Immunodeficiency Virus (HIV) and Universal Access remains a dream for millions of people. By end 2008, 4 million people were on treatment, however, over 5 million needed treatment and in 2007 there were 2.7 million new infections. Without significant improvement in prevention, we are unlikely to meet universal access targets including the growing demand for highly active antiretroviral treatment (HAART). This review examines HAART as a potential tool for preventing HIV transmission

Recent findings: describe the main themes in the literature covered by the article— We discuss recent scientific evidence regarding the treatment and prevention gap, importance viral load and HIV transmission, HAART and HIV transmission, when to start, HIV counseling and testing, modeling results and next steps.

Summary: describe the implications of the findings for clinical practice or research —HAART has considerable treatment and prevention benefits and it needs to be is considered as a key element of combination prevention. To explore HAART as an effective prevention strategy we recommend further evaluation of human rights and ethical considerations, clarification of research priorities and exploration of feasibility and acceptability issues.

Keywords

HAART; HIV; prevention; universal access; modeling

Introduction

After over 27 years it is important to pause and consider the devastating extent of the HIV pandemic.[1] Over 25 million people have died and an estimated 33 million people are

Address correspondence and reprint requests to: Reuben Granich, MD, MPH, Antiretroviral Treatment and HIV Care Unit, Department of HIV/AIDS, World Health Organization, Avenue Appia 20, CH-1211, Geneva 27, Tel: 41 22 791 1459, Fax: 41 22 791 4834, granichr@who.int.

Disclaimer
The opinions and statements in this article are those of the authors and do not represent the official policy, endorsement or views of the World Health Organization

Conflict of interests
None of the authors have conflicts of interest to declare.

living with HIV.[2] In 2008, about 68% of people living with HIV were in sub-Saharan Africa with around 35% in 8 countries alone.[2] HIV is the strongest risk factor for tuberculosis (TB) and an estimated 1.4 million people living with HIV developed TB causing 500,000 (23%) of total HIV-related deaths. [3*] In 2005 and 2009 the G8 met in Scotland and Italy and committed to achieving Universal Access to HIV prevention, care and treatment by 2010. [2] However, Universal Access remains a dream for millions of people and faces serious technical, economic and political challenges on a number of fronts. [2]

There has been an unprecedented investment in confronting the HIV pandemic--UNAIDS estimates $13.8 billion in 2008. [4] One of the major challenges facing us is how to not only sustain but expand our response to the HIV epidemic in the face of the worst economic crisis since the 1930's. The significance and implications of the economic problem are at times beyond comprehension. Over $14.5 trillion, or 33%, of the value of the world's companies has been wiped out and US taxpayers alone will spend some $9.7 trillion in bailout packages and plans.[5] The economic disaster is being felt world-wide and has already impacted investment in international and national public health.

Treatment and prevention gap

The imperative of providing life-saving ART is now undisputed and there is a pressing need for both increased investment and more efficient use of funding. By end 2008, 4 million people were on HAART.[2] Despite this remarkable achievement, over 5 million needed treatment and in 2007 there were 2.7 million new infections.[2] Around 23 million people were waiting, mostly unknowingly, to become treatment-eligible, sicken or die. The estimated coverage of antiretroviral therapy reached 42% in low and middle-income countries using the lower 200 CD4 count eligibility criteria.[2] If we do not dramatically reduce HIV incidence it is unlikely that we will be able to meet universal access targets including the growing demand for HAART.

The human rights gap

The HIV epidemic highlights the serious lack of equity and human rights in our global public health response. The millions of people living with or at risk for HIV without access to HIV prevention, treatment and care can be interpreted a serious breach of the fundamental right to health care.[6] Coercion and other mandatory approaches to addressing the HIV epidemic have often had perverse negative outcomes. Engaging the community as a meaningful partner in the design and implementation of HIV programmes is critical, particularly when the potential for stigma and human rights violations exist.[7] The existing stark economic disparities may exacerbate human rights issues and could further widen the increasingly divergent approaches to HIV prevention, care and treatment that are seen between rich and poor countries. [8] [9]

If it's broken then we should fix it…

Stopping the HIV epidemic remains elusive in most settings and there is a need to re-examine our current approaches to stopping HIV. Combination prevention includes evidence-based interventions to address behavioral change, HAART, other biomedical strategies, and structural, social justice and human rights interventions. [10] [11] Of 27 randomized controlled trials of different biomedical interventions including vaccines, microbicides, and herpes suppression trials, 22 failed to show efficacy.[12] [13] [14] Positive trials include those for male circumcision, and the STI intervention trial in Mwanza, Tanzania, over a decade ago, of limited generalizability. [14] Users of the microbicide gel Pro 2000 had a non-statistically significant 30% reduction in HIV incidence.[15*] Pre-exposure prophylaxis (PrEP) is being assessed in ten ongoing or planned international

randomized controlled trials with results expected in 2010. Although the concept of PrEP is promising, it will undoubtedly be difficult to give drugs to HIV-uninfected persons when many people are dying from lack of access to HAART and may also face operational challenges around the need to repeat HIV testing to ensure that only those without HIV receive mono or dual therapy. A vaccine may provide an important future intervention, [16*] however, the overall situation has prompted many people to consider the potential prevention role of HAART. [17] [18**]

Scientific evidence for HAART as prevention of HIV transmission

There is increasingly strong scientific evidence for HAART as prevention of HIV transmission. HIV transmission only occurs from people with HIV, the greatest risk factor for HIV transmission is the viral load, and lowering the viral load is essential to interrupting transmission. [1] [19]Viral load predicts the risk of sexual transmission of HIV-1 which is rare among persons with levels of less than 1500 copies of HIV-1 RNA per milliliter. [19] [20]HAART dramatically lowers viral load and numerous observational studies have demonstrated its potential for prevention of HIV transmission. [21] [22]HAART with couples counseling in Uganda reduced transmission by 98%. [22] A 2009 meta-analysis including 11 cohorts (5021 heterosexual couples) found zero risk of sexual transmission while on HAART for HIV-1 ribonucleic acid below 400 copies (upper confidence limit of 1.27 per 100 years). [23] A recent randomized controlled study of genital herpes simplex virus treatment among long-term, HIV-serodiscordant heterosexual couples in Africa found a 92% reduction in transmission if the HIV-positive partner was on HAART. [24] The proportion of couples who had unprotected sex actually decreased when the HIV-positive partner started treatment, allaying fears about behavior change. [24**]

Prevention of maternal-to-child transmission offers further proof of concept that HAART interrupts HIV transmission. In the United States, perinatal AIDS cases have been virtually eliminated most likely due to the implementation of guidelines for the universal counseling, voluntary HIV testing and HAART for pregnant women and newborn infants. [25] In 2008, the majority of the 430,000 new pediatric HIV infections were in sub-Saharan Africa where there is recent evidence that HAART can be used to decrease transmission to 1%. [26*]

Studies also suggest a potential for the community-level impact of HAART on HIV transmission. In British Columbia a decrease in community plasma HIV RNA concentrations and HIV incidence among injecting drug users is associated with HAART use [27**] In San Francisco between 2004 and 2008, the number of HIV diagnoses fell by 45%, the average viral load amongst the HIV-positive population by 40%, and the actual HIV incidence fell by one-third between 2006 and 2008. [28**] In Taiwan a 53% reduction in new HIV cases was associated with free access to HAART. [29**]

When to start?

Although there are over four million people on ART, it is not known with certainty how early to start HAART. In sub-Saharan Africa people start HAART very late at a median CD4 count of around 100 and despite progress with improving earlier access, mortality remains markedly higher when compared with other contexts. [30**] [31]Starting late sharply increases the risk of death even for patients on HAART and is associated with the time spent below 200 CD4+ cells per cubic mm. [32**] [33**] Even after testing positive and entering care, one South African study found that patients with higher CD4 cell counts are being monitored too infrequently for the timely start of treatment and 25% of people die waiting for HAART. [34**] Although mortality rates at the higher CD4 levels are lower, they are not zero, and may represent a significant impact on morbidity and mortality. In Zimbabwe, HIV mortality within 24 months postpartum in the absence of HAART was 54

times higher for those with CD4 cell counts less than 200 cells/ml, 5.4 times higher for 400-600, and the hazard remained elevated at 6.2 for greater than 600. [35**] North American cohort data showed a 94% increase in mortality for those who started treatment below CD4 level of 500 when compared to those who started earlier. [36**] Europe and North America cohorts including over 40,000 patients showed that starting treatment earlier reduced the risk of acquired immunodeficiency syndrome or death with those starting before reaching 450 having the most benefit. [30] Other cohort studies also suggest that starting earlier is better and the evidence increasingly points to the damaging effects of HIV even at higher CD4 count levels and the negative effects of letting CD4 counts drop too low. [37] [39] [40**] [41] HAART has a significant role to play in preventing TB morbidity, transmission and mortality. In a randomized clinical trial of 642 patients co-infected with HIV and tuberculosis in South Africa starting HAART earlier during tuberculosis therapy reduced mortality rates by 56 percent. [42**] To prevent TB we may have to intervene with HAART earlier before people living with HIV spend too long in the CD4+ “death zone” (<500 CD4 cells) for tuberculosis. [32] [33] Recognising this, WHO recently revised it’s guidelines to recommend ART for all with less than 350 CD4 cells. [43**]

Trial data also points in the direction of an earlier start. The CIPRA HT 001 randomized clinical trial in Haiti was stopped by the Data Safety Monitoring Board since there were significantly fewer deaths and cases of TB in patients who started HAART earlier between 200 and 350.[44**] Survival curves show a 47% reduced progression or death in patients receiving immediate as opposed to deferred HAART in ACTG A 1564. [45*] The SMART trial and more recent work have suggested that starting earlier was superior and found that HIV may be associated with serious non-AIDS defining events including cardiovascular, renal, and liver disease and non-AIDS malignancies. [37] [38] [46*] The growing evidence suggests that HIV infection is likely a chronic inflammatory disease process provides additional rationale for an earlier start of HAART.

People living with HIV will eventually need HAART and the question is how long to wait until a person is immunocompromised enough to be eligible for treatment. Data from 30 international studies and 16 cohorts of untreated adults found relatively low CD4 levels after HIV infection and a fairly rapid progression to CD4 thresholds such as 500, 350 and 200. [47**] The time to eligibility was variable and in some settings only a few years after HIV infection. [47**] From this perspective and assuming access to HAART, decisions whether to start at 200, 350 or 500 represent a few years earlier in the course of a much longer life span. Guidelines written for wealthier countries recommend starting people earlier before severe immunocompromised and use factors such as CD4 decline, viral replication, and discordant couple status as potential eligibility criteria even at higher CD4 counts. [48] The recently revised WHO guidelines also advise and earlier start. [43] Our challenge is to narrow the current treatment gulf that is largely based on available resources.

HIV counselling and testing

Regardless of when people should start HAART, universal access to prevention, care and treatment will require that millions of people with HIV learn their status. Despite considerable efforts to expand access to HIV testing, an estimated 80% of people living with HIV in sub-Saharan Africa do not know their status and 90% do not know their partners status. [2] [49]In Kenya, a leader in improving access for HIV counseling and testing, 57% of people eligible for HAART by Kenyan CD4 count criteria have no idea that they have HIV. [50**] However, 92% of those who knew their status and were eligible were on HAART. [50**] HIV counseling and testing itself—particularly when it includes couples counseling--is a remarkably effective prevention intervention.[22] [51] [52] [53] Community-based efforts, including home-based couples counseling and testing, have considerable promise. In a district in Western Kenya, a private sector company with local

NGOs, Centers for Disease Control Kenya, and the Ministry of Health was able to test 41,040 or 80% of the men and women between 15 and 49 during a seven day campaign. [54]

Modelling results

Models help us to better understand what we think we know and perhaps most importantly what we need to find out. Our model focused on a generalized HIV epidemic setting largely driven by heterosexual sex and used data from South Africa, Uganda, Malawi and elsewhere. [18**] It builds on and extends, earlier analyses suggesting that rapid scale-up of conventional HAART approaches could significantly reduce mortality [55]and have a substantial impact on HIV incidence. [56], [17] The modeled universal voluntary HIV testing and immediate HAART strategy with combined prevention interventions resulted in a 95% reduction in HIV incidence in 10 years—a reduction from 15-20,000 per million population to 1000 per million. The prevalence becomes less than 1% by 2050. [18**] HAART for all less than 350, as per current WHO recommendations, could save nearly 2.41 million lives while the universal voluntary HIV testing combined prevention approach nearly triples that number to 7.35 million but we are left with a persistent epidemic. [18**] A rough costing for the strategies is considerably less than what UNAIDS projected for universal access to prevention, care and treatment. [18**] Current work includes an in-depth analysis of the economic impact of ART including human rights and campaign program elements and further modelling on the impact of ART on TB which suggests a potential 60% reduction in incidence (unpublished data).

Modeling ‘test and treat’ for Washington, D.C. concluded that the strategy could potentially decrease the number of new HIV infections there by as much as 26% over ten years and work in San Francisco suggests that incident infections could be reduced by 91%.[57,58] Other mathematical modeling studies have reviewed assumptions and to examined ‘test and treat’ in other contexts but a full discussion is beyond the scope of this article. [57**] [58**] [59*]; [60*] [61*,62] [63*] Models are perhaps most useful when used to examine the potential impact of public health interventions and to discuss programmatic targets for maximal impact. Models are sensitive to key assumptions and when using more pessimistic parameters or a different context the results are predictably less optimistic. [59*,60*] [61*, 62] One modelling group using hypothetical assumptions raised the spectre of widespread resistance [62] but actual data from programs providing HAART and population-based threshold studies suggest that these claims may not reflect the actual situation. [64] [65] [66] [67] [68**] Resistance is of course a serious concern and WHO is working with stakeholders to monitor the situation through the The WHO/HIVResNet HIVDR Laboratory Network which currently includes over 30 laboratories covering the WHO’s African, South-East Asia, Western Pacific, and the Caribbean Regions [69] [70]Although modelling is important, research studies and field trials will need to examine the key thresholds for program performance raised in the supporting information of the recent *Lancet* paper [18**] and in subsequent articles by the modelling community. [57**] [58**] [59*]; [60*] [61*,62] [63*]

Next steps

While expanding HAART to meet universal access targets, there is a need for further scientific evaluation and discussion to define the requirements for public health decision making on how to best use of HAART for prevention and control of HIV/AIDS. [17,18,**71**,72] In November 2009 WHO held two HAART for prevention stakeholders meetings to explore human rights and ethical considerations, clarify research priorities and review feasibility and acceptability issues (the presentations, list of participants and outcomes of the meeting are available at http://www.who.int/hiv/events/artprevention/). WHO and its collaborators are engaged in further modeling on the impact of HAART on

TB, the relative importance of drug resistance and other assumptions, the effect of combination PrEP and 'test and treat', effects on PMTCT and an in-depth economic analysis of the various strategies. There are a number of planned field trials and analyses including ongoing and planned work in Washington District of Columbia and the Bronx in New York City, [73,74] Vancouver, British Columbia, [75**] San Francisco California, [28]Botswana, [76] and Kwa-Zulu Natal, South Africa.[77] Scientific and community opinion leaders have called for expansion of access to treatment during further research on HAART as prevention. [17,71,**77]Funding opportunities are increasing and more data on this important topic should be available in the near future. [17,71,**77]

Conclusion

HIV is an infectious disease and with the right interventions it can be controlled and possibly even eliminated. Without a considerable effort to achieve Universal Access, millions of people will die before accessing HAART. HAART has considerable benefit both as treatment and prevention and it is likely that it will be increasingly considered as a key element of combination prevention.

References

1. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983; 220:868–871. [PubMed: 6189183]
2. WHO. Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector. 2008
*3. WHO. Global tuberculosis control : epidemiology, strategy, financing WHO/HTM/TB/2009.411. Geneva, Switzerland: 2009. http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf. Yearly WHO surveillance report that describes global TB control progress
4. UNAIDS. Financial resources required to achieve universal access to HIV prevention, treatment, care and support. Geneva, Switzerland: 2007. http://data.unaids.org/pub/Report/2007/20070925_advocacy_grne2_en.pdf
5. [March 13, 2010] Global Issues: Social, Political, Economic and Environmental Issues That Affect Us All. http://www.globalissues.org/article/768/global-financial-crisis#Thefinancialcrisisandthedevelopingworld
6. United Nations Universal Declaration of Human Rights (Article 25). 1948. http://www.un.org/en/documents/udhr/
7. UNHCR. HIV/AIDS and Human Rights: International Guidelines Revised Guideline 6: Access to prevention, treatment care and support. Geneva, Switzerland: 2003. http://whqlibdoc.who.int/publications/2002/9291730254.pdf
8. UNAIDS. Handbook for legislators on HIV/AIDS, Law and Human Rights. Geneva, Switzerland: 1997. http://www.ipu.org/PDF/publications/aids_en.pdf
9. UNHCR. Handbook on HIV and Human Rights for National Human Rights Institutions. Geneva, Switzerland: 2007. http://data.unaids.org/pub/Report/2007/jc1367-handbookhiv_en.pdf
10. WHO. Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva, Switzerland: 2008. http://www.who.int/hiv/pub/prev_care/OMS_EPP_AFF_en.pdf
11. UNAIDS. Practical Guidelines for Intensifying HIV Prevention - towards universal access - UNAIDS/07.07E / JC1274E 2007. Geneva, Switzerland: 2007. http://data.unaids.org/pub/Manual/2007/jc1274-towardsuniversalaccess_en.pdf
12. Desrosiers, R. Scientific Obstacles to an Effective HIV Vaccine. presented at 15th Conference on Retroviruses and Opportunistic Infections (CROI 2008); 2008; CROI Abstract 91
13. Weiss RA. Special anniversary review: twenty-five years of human immunodeficiency virus research: successes and challenges. Clin Exp Immunol. 2008; 152:201–210. [PubMed: 18373700]

14. Cohen J. HIV/AIDS. The great funding surge. Science. 2008; 321:512–519. [PubMed: 18653876]

*15. Karim, S. Safety and effectiveness of vaginal microbicides BufferGel and 0.5% PRO 2000/5 gel for the prevention of HIV infection in Women: Results of the HPTN035 Trial. The 16th Conference on Retroviruses and Opportunistic Infections; 8-11 February, 2009; Montreal, Canada. http://www.retroconference.org/2009/Abstracts/36659.htm. Preliminary data on one of the largest and most important microbicide trials

*16. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premsri N, Namwat C, de Souza M, Adams E, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009; 361:2209–2220. Thai vaccine trial that showed that the vaccine regimen may reduce the risk of HIV infection in a community-based population with largely heterosexual risk. Although the results show only a modest benefit, they offer insight for future research. [PubMed: 19843557]

17. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, Harrigan PR. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. Lancet. 2006; 368:531–536. [PubMed: 16890841]

**18. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009; 373:48–57. WHO modeling paper that examines potential for universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission in a southern african setting. [PubMed: 19038438]

19. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T, Gray RH. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. 2000; 342:921–929. [PubMed: 10738050]

20. Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, Kawichai S, Tanan P, Duerr A, Nelson KE. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. J Acquir Immune Defic Syndr. 2002; 29:275–283. [PubMed: 11873077]

21. Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr. 2005; 40:96–101. [PubMed: 16123689]

22. Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, Coutinho A, Liechty C, Madraa E, Rutherford G, 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. [PubMed: 16327323]

23. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009; 23:1397–1404. [PubMed: 19381076]

**24. Donnell, D. ART and Risk of Heterosexual HIV-1 Transmission in HIV-1 Serodiscordant African Couples: A Multinational Prospective Study. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 136. http://www.retroconference.org/2010/Abstracts/39222.htm. Important early results from international HSV suppression trial that demonstrated that discordant couples who were on ART were very unlikely to transmit HIV; additionally it also showed through genotyping that around 25% of new infection came from outside the discordant couple

25. Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. Morb Mortal Wkly Rep. 2006; 55:592–597.

*26. Shapiro, R. A randomized trial comparing highly active antiretroviral therapy regimens for virologic efficacy and the prevention of mother-to-child HIV transmission among breastfeeding women in Botswana. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 19-22 July 2009; Cape Town, South Africa. http://www.ias2009.org/pag/Abstracts.aspx?SID=2435&AID=3821. Additional proof of concept that ARVs, if used in an adequate and timely fashion, have the potential to reduce mother to child transmission to very low levels

**27. Wood E, Kerr T, Marshall BD, Li K, Zhang R, Hogg RS, Harrigan PR, Montaner JS. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. BMJ. 2009; 338:b1649. Compelling and

pioneering community-based study demonstrating that ART can reduce community viral load and HIV transmission among injecting drug users. [PubMed: 19406887]

**28. Das-Douglas, M. Decreases in Community Viral Load Are Associated with a Reduction in New HIV Diagnoses in San Francisco. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 33. http://www.retroconference.org/2010/Abstracts/38232.htm. Additional evidence from San Francisco setting, where ART and HIV testing coverage is among the highest in the world, that ART influences community viral load and HIV transmission

**29. Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, Wang JD, Chuang CY. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. J Infect Dis. 2004; 190:879–885. Pioneering community-based study examining effects of providing free ART on HIV transmission. ART provision is associated with decreased HIV transmission. [PubMed: 15295691]

**30. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, Funk MJ, Geskus RB, Gill J, Dabis F, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009; 373:1352–1363. Important collection of cohort studies that demonstrate that sarting ART earlier may be of significant benefit. How early remains open question but this work supports higher than current 200, 250 or 350 CD4 level recommendations. [PubMed: 19361855]

31. Brinkhof MW, Dabis F, Myer L, Bangsberg DR, Boulle A, Nash D, Schechter M, Laurent C, Keiser O, May M, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bull World Health Organ. 2008; 86:559–567. [PubMed: 18670668]

**32. Lawn SD, Little F, Bekker LG, Kaplan R, Campbel E, Orrell C, Wood R. Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. AIDS. 2009; 23:335–342. This important work is part of a body of work from this group demonstrating that the lower one's CD4 count the higher risk for morbidity and mortality and in particular from TB. National HIV programmes in resource-limited settings should be designed to minimize the time patients spend with CD4 cell counts less than 200 cells/microl both before and during ART. [PubMed: 19114870]

**33. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. Aids. 2009; 23:1717–1725. This important work is part of a body of work from this group demonstrating that the lower one's CD4 count the higher risk for morbidity and mortality and in particular from TB. This group coined phrase "death zone" for CD4 less than 500 level and conclued that TB prevention would be improved by ART policies that minimized the time patients spend with CD4 cell counts below a threshold of 500 cells/microl. [PubMed: 19461502]

**34. Ingle, S. Pre-treatment Mortality and Probability of Starting ART in Patients Enrolled in the Free State ARV Program, South Africa: Implications for Treatment Guidelines. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 108. http://www.retroconference.org/2010/Abstracts/37166.htm. Interesting work that illustrates that current policies recommending that people wait for further CD4 decline may result in considerable mortality on the waiting list

**35. Hargrove JW, H J. Mortality among HIV-positive postpartum women with high CD4 cell counts in Zimbabwe. AIDS. 2010; 24:F11–14. Major study that most people likely missed that illustrates that in post-partum women living with HIVthere is increased morbidity and mortality at all CD4 levels and that risk never returns to baseline fo those who are hIV negative. Directionally similar to other cohort studies that call into question waiting to start HAART until severely immunocompromised. [PubMed: 20095074]

**36. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, Hogg RS, Deeks SG, Eron JJ, Brooks JT, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009; 360:1815–1826. Seminal look at North American cohorts that suggests that starting earlier before 350 and/or 500 may have a significant mortality benefit. Among patients in the deferred-therapy group, there was an increase in the risk of death of 94%. The early initiation of antiretroviral therapy before the CD4+ count fell below two prespecified

thresholds significantly improved survival, as compared with deferred therapy. [PubMed: 19339714]

37. El-Sadr WM, Grund B, Neuhaus J, Babiker A, Cohen CJ, Darbyshire J, Emery S, Lundgren JD, Phillips A, Neaton JD. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial. Ann Intern Med. 2008; 149:289–299. [PubMed: 18765698]

38. Lundgren JD, B A, El-Sadr W, Emery S, Grund B, Neaton JD, Neuhaus J, Phillips AN. Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up. J Infect Dis. 2008; 197:1145–1155. [PubMed: 18476293]

39. Castilla J, S P, De La Fuente L, Noguer I, Guerra L, Parras F. Late diagnosis of HIV infection in the era of highly active antiretroviral therapy: consequences for AIDS incidence. AIDS. 2002; 16:1945–1951. [PubMed: 12351955]

**40. Walensky RP, Wolf LL, Wood R, Fofana MO, Freedberg KA, Martinson NA, Paltiel AD, Anglaret X, Weinstein MC, Losina E. When to start antiretroviral therapy in resource-limited settings. Ann Intern Med. 2009; 151:157–166. Work focused on South Africa that suggests that earlier initiation of ART in South Africa will probably reduce morbidity and mortality, improve long-term survival, and be cost-effective. While awaiting trial results, treatment guidelines should be liberalized to allow initiation at CD4 counts less than 350 (earlier than was recommended at the time of the study). [PubMed: 19620143]

41. Jaen A, Esteve A, Miro JM, Tural C, Montoliu A, Ferrer E, Riera M, Segura F, Force L, Sued O, et al. Determinants of HIV progression and assessment of the optimal time to initiate highly active antiretroviral therapy: PISCIS Cohort (Spain). J Acquir Immune Defic Syndr. 2008; 47:212–220. [PubMed: 18297762]

**42. Abdool Karim SS, N K, Grobler A, Padayatchi N, Baxter C, Gray A, Gengiah T, Nair G, Bamber S, Singh A, Khan M, Pienaar J, El-Sadr W, Friedland G, Abdool Karim Q. Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy. N Engl J Med. 2010; 362:697. Important study which confirms that waiting until patients with TB complete TB treatment before starting ART causes poor outcomes; earlier start of ART during TB treatment is beneficial and WHO ART guidelines now recommend starting ART as soon as possible for all TB patients regardless of CD4 count. [PubMed: 20181971]

**43. [March 14, 2010] W: Rapid Advice, Antiretroviral therapy for HIV infection in adults and adolescents. 2009. Available from: http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. Updated WHO ART guidelines which recommend starting ART for those less than 350

**44. NIAID. [March 13th, 2010] website http://www3.niaid.nih.gov/news/QA/CIPRA_HT01_qa.htm. Additional evidence that starting HAART early has benefits. During its May 28 review, the DSMB found overwhelming evidence that starting ART at CD4+ T cell counts between 200 and 350 cells/mm3 improves survival compared with deferring treatment until CD4+ T cells drop below 200

*45. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, Hogg E, Komarow L. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One. 2009; 4:e5575. Clinical trial illustrating that early ART resulted in less AIDS progression/death with no increase in adverse events or loss of virologic response compared to deferred ART. These results support the early initiation of ART in patients presenting with acute AIDS-related OIs, absent major contraindications. [PubMed: 19440326]

*46. Sigel, K. HIV Infection Is an Independent Risk Factor for Lung Cancer. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 30. http://www.retroconference.org/2010/Abstracts/38365.htm. Additional evidence that HIV is associated with non-AIDS related morbidity and mortality

**47. Korenromp EL, Williams BG, Schmid GP, Dye C. Clinical prognostic value of RNA viral load and CD4 cell counts during untreated HIV-1 infection--a quantitative review. PLoS One 2009. 4:e5950. Important overlooked study that illustrates the incredible variablity in starting CD4 counts and CD4 count decline which, if taken seriously, calls into question our ability to base ART eligibility on CD4 counts as they vary from setting to setting. Study also illustrates that for

some patients in some settings CD4 decline is quite rapid which has implications for CD4 monitoring for eligibility.

48. Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, Fischl MA, Gatell JM, Hirsch MS, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. Jama. 2008; 300:555–570. [PubMed: 18677028]

49. Bunnell R, Mermin J, De Cock KM. HIV prevention for a threatened continent: implementing positive prevention in Africa. JAMA. 2006; 296:855–858. [PubMed: 16905790]

**50. Mohammed, I. HIV Prevalence and Unmet Need for HIV Testing, Care and Treatment in Kenya: Results of a Nationally Representative Survey. CROI. 2009. http://www.retroconference.org/2009/Abstracts/36616.htm. Important early look at Kenya HIV counseling and testing, CD4 and ART coverage among other things. Should produce a number of significant papers and policy decisions. Among HIV-infected married/cohabitating persons, 43.8% had an uninfected partner. Among all HIV-infected persons, 81.3% did not know their current HIV status; 54.4% had never been tested and 26.9% reported being uninfected based on their last test. Among those aware of their status, 74.9% were taking cotrimoxazole and 92.1% were on ART. In Kenya a minority of people know their HIVstatus but when it is known people do access ART

51. Dunkle KL, Stephenson R, Karita E, Chomba E, Kayitenkore K, Vwalika C, Greenberg L, Allen S. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. Lancet. 2008; 371:2183–2191. [PubMed: 18586173]

52. Malamba SS, Mermin JH, Bunnell R, Mubangizi J, Kalule J, Marum E, Hu DJ, Wangalwa S, Smith D, Downing R. Couples at risk: HIV-1 concordance and discordance among sexual partners receiving voluntary counseling and testing in Uganda. J Acquir Immune Defic Syndr. 2005; 39:576–580. [PubMed: 16044010]

53. Allen S, Tice J, Van de Perre P, Serufilira A, Hudes E, Nsengumuremyi F, Bogaerts J, Lindan C, Hulley S. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. Bmj. 1992; 304:1605–1609. [PubMed: 1628088]

54. New York Times: A Company Prospers by Saving Poor People's Lives. Feb 2. 2009 http://www.nytimes.com/2009/02/03/health/research/03prof.html?_r=1&scp=2&sq=Mikkel+Frandsen&st=nyt

55. Walensky RP, Wood R, Weinstein MC, Martinson NA, Losina E, Fofana MO, Goldie SJ, Divi N, Yazdanpanah Y, Wang B, et al. Scaling up antiretroviral therapy in South Africa: the impact of speed on survival. J Infect Dis. 2008; 197:1324–1332. [PubMed: 18422445]

56. Velasco-Hernandez JX, Gershengorn HB, Blower SM. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? Lancet Infect Dis. 2002; 2:487–493. [PubMed: 12150848]

**57. Walensky, R. Test and treat DC: modeling the impact of a comprehensive HIV strategy in the US Capitol. at 5th IAS Conference on HIV Pathogenesis Treatment and Prevention; 19-22 July 2009; Abstract 88. http://www.ias2009.org/pag/Abstracts.aspx?AID=3748. Modeling looking at potential impact of test and treat in DC which shows that compared to background screen and ART at ≤ 350/μl (current standard, bold), annual testing with immediate ART increases HIV+ life expectancy by 2.8 years and decreases secondary cases by 26% over 10 years

**58. Charlebois, E. Effect of Expanded ART Strategies on the MSM HIV Epidemic in San Francisco. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 996. http://www.retroconference.org/2010/Abstracts/39042.htm. Modeling looking at potential impact of 1) ART treatment for all adults currently in care at CD4<500, 2) ART for all adults in care regardless of CD4 count, 3) ART for all adults in care plus community-wide annual HIV testing, comparing these strategies to the current practice of ART for CD4 <350 in San Francisco which showed a percent reduction in incident infections with the 3 strategies of 49%, 71%, and 91% over the first 10 years for strategies, respectively. The number of new infections averted by the 3 strategies is estimated at 3559, 5153, and 6560 at 10 years

*59. Garnett GP, Baggaley RF. Treating our way out of the HIV pandemic: could we, would we, should we? Lancet. 2009; 373:9–11. Commentary regarding potential value of ART for prevention. [PubMed: 19038439]

*60. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. AIDS. 24:729–735. Model uses less optimistic adherence assumptions and shows that a test-and-treat intervention that does not reach full implementation or coverage could, perversely, increase long-term ART costs. Interventions that prevent new infections through ART scale-up may hold substantial promise. [PubMed: 20154580]

*61. Scott, C. Test and Treat: Forecasting the clinical and epidemiological impact of expanded HIV screening and immediate ART in sub-Saharan Africa. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 964. http://www.retroconference.org/2010/Abstracts/39676.htm. Examined adherence assumption in test and treat model and showed that it is sensitive to adherence levels as many people will end up on ART

62. Smith RJ, Okano JT, Kahn JS, Bodine EN, Blower S. Evolutionary dynamics of complex networks of HIV drug-resistant strains: the case of San Francisco. Science. 327:697–701. [PubMed: 20075214]

*63. Vijver, Dvd. Potential Impact of Recent Infections, HIV Testing and Start of Antiretroviral Drugs at a CD4 of <350 on the HIV Epidemic in a Rural Area in Zambia: A Mathematical Model. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 963.http://retroconference.org/2010/Abstracts/37500.htm. Modeled test and treat in Zambia and showed that increased testing and starting treatment at CD4<350 can substantially reduce the HIV incidence in Macha over a period of 10 years. The impact on HIV prevalence is smaller, as patients will survive for a longer period of time. The HIV epidemic can only be eliminated if we succeed in timely identification of recently infected patients

64. Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antivir Ther. 2008; 13(Suppl 2):25–36. [PubMed: 18575189]

65. Kamoto K, A-G J. Surveillance of transmitted HIV drug resistance with the World Health Organization threshold survey method in Lilongwe, Malawi. Antivir Ther. 2008; 13(Suppl 2):83–87. [PubMed: 18575195]

66. Nguyen HT, Duc NB, Shrivastava R, Tran TH, Nguyen TA, Thang PH, McNicholl JM, Leelawiwat W, Chonwattana W, Sidibe K, et al. HIV drug resistance threshold survey using specimens from voluntary counselling and testing sites in Hanoi, Vietnam. Antivir Ther. 2008; 13(Suppl 2):115–121. [PubMed: 18575200]

67. Somi GR, Kibuka T, Diallo K, Tuhuma T, Bennett DE, Yang C, Kagoma C, Lyamuya EF, Swai RO, Kassim S. Surveillance of transmitted HIV drug resistance among women attending antenatal clinics in Dar es Salaam, Tanzania. Antivir Ther. 2008; 13(Suppl 2):77–82. [PubMed: 18575194]

**68. Gill VS, Lima VD, Zhang W, Wynhoven B, Yip B, Hogg RS, Montaner JS, Harrigan PR. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. Clin Infect Dis. 2010; 50:98–105. Study of temporal changes of drug resistance from program data which suggests an increasing effectiveness of highly active antiretroviral therapy at the populational level. The vast majority of treated patients in British Columbia now have either suppressed plasma viral load or drug-susceptible HIV-1, according to their most recent test results, with decrease in drug resistance. [PubMed: 19951169]

69. Bertagnolio S, Derdelinckx I, Parker M, Fitzgibbon J, Fleury H, Peeters M, Schuurman R, Pillay D, Morris L, Tanuri A, et al. World Health Organization/HIVResNet Drug Resistance Laboratory Strategy. Antivir Ther. 2008; 13(Suppl 2):49–57. [PubMed: 18575191]

70. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. Antivir Ther. 2008; 13(Suppl 2):1–13. [PubMed: 18578063]

**71. Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. Jama. 2009; 301:2380–2382. Commentary outlining importance and NIH ART for Prevention research priorities. [PubMed: 19509386]

72. De Cock K. Kevin De Cock: guiding HIV/AIDS policy at WHO. Interview by Priya Shetty. Lancet Infect Dis. 2008; 8:98–100. [PubMed: 18222161]

73. Castel, A. Monitoring the Impact of Expanded HIV Testing in the District of Columbia Using Population-based HIV/AIDS Surveillance Data. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 34. http://www.retroconference.org/2010/Abstracts/38192.htm

74. Okie, S. [March 14, 2010] Fighting H.I.V., a Community at a Time. New York Times. Oct 26. 2009 http://www.nytimes.com/2009/10/27/health/27hiv.html

**75 1. Montaner, J. Association of Expanded HAART Coverage with a Decrease in New HIV Diagnoses, Particularly among Injection Drug Users in British Columbia, Canada. at 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA. 2010; Abstract 88. http://www.retroconference.org/2010/Abstracts/39866.htm. Work that discusses association between coverage and decreased incidence and plans to use ART as prevention as major cornerstone of HIV control in Vancouver, Canada

76. McLaughlin, L. [March 14, 2010] A ‘test and treat’ approach to fighting HIV Boston Globe. Feb 26. 2010 http://www.boston.com/bostonglobe/editorial_opinion/oped/articles/2010/02/26/a_test_and_treat_approach_to_fighting_hiv/

77. De Cock KM, Crowley SP, Lo YR, Granich RM. Williams BG: Preventing HIV transmission with antiretrovirals. Bull World Health Organ. 2009; 87:488–488A. [PubMed: 19649357]