

HIV - Preventing New Infections: New Options, Readjusted Approaches

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Thesis (Summary)

- As of 2013-14, several separate new developments have coalesced to permit a balanced prevention strategy for HIV
 - Emphasizing methods that work directly with infected patients and their partners (control at the source), while not abandoning traditional methods directed toward high-risk populations
 - Incorporating methods that reduce exposure, and others that mitigate exposure risks (harm reduction)
 - Permitting calculation of cost-effectiveness and risk-benefit of various combinations of interventions
- Now is a time for action to implement strategy ₂

Three approaches to prevention of communicable diseases

- Vaccines (influenza, hepatitis B)
 - Not available for HIV
- General measures directed to populations at risk
 - Education, screening, barriers, behavior change
 - Mainstay for HIV for over 30 years, 1981-present
- Control at source (infected person and contacts)
 - Mainstay for syphilis, tuberculosis
 - For HIV, facilitated by HIV reporting (since 2006)
 - Challenged by weak local public health infrastructure; use for HIV controversial for many years and remains so in some communities

Evolution 1996-2012

- 1996:
 - HAART becomes available: 3-drug combinations
 - Hattis-Jason proposal to study reduction of HIV infectiousness with medication; supported by California Medical Association
- 1998:
 - PCRS guidelines (partner counseling and referral services; different from partner services for other STDs)
 - National policy process begins (CDC, IOM, APHA)
 - Beyond AIDS founded, supports name reporting, opposes AIDS exceptionalism
 - New York name reporting and partner notification law
 - Legislative sponsor becomes a leader of Beyond AIDS
- 2001:
 - CDC initiates program concepts for prevention among positives
 - Guidelines issued in MMWR 2003, “Prevention with Positives”

Evolution 1996-2012, contd.

- 2006:
 - Final states adopt name reporting; Ryan White funding incentive to states for complete HIV reporting begins
 - Victory for Beyond AIDS after 8-year campaign
 - CDC recommends universal HIV screening with opt-out oral consent
- 2008:
 - CDC issues unified partner services guidelines for HIV, syphilis, gonorrhea, chlamydia
 - First modeling in Canada suggests that getting more infected people into treatment would reduce incidence rates (Lima et al., JID v. 198:59-67)

Evolution 1996-2012, contd.

- 2009:
 - Modeling study predicts major reduction in incidence for South Africa if treatment offered immediately
(Granich et al., Lancet v. 373:48-57, 1/3/09)
- 2011:
 - HPTN 052 study shows 96% reduction in infectiousness of infected persons with undetectable viral loads
(Cohen et al., NEJM, v. 365:493-505, 8/11/11)

Evolution 1996-2012, contd.

- 2012:
 - CDC distributes “Prevention is Care” kits to providers for use with positives
 - Predated 2012 treatment guidelines; do not include offering immediate treatment, maintaining adherence, or suppressing/monitoring viral load (2003 MMWR rec’s)
(<http://www.cdc.gov/actagainstaids/resources/pic/index.html>)
 - HHS/NIH (March) and IAS-USA (July) antiretroviral treatment guidelines recommend offering antiretroviral treatment to all infected persons regardless of CD4 count
 - Previous gradual raising of CD4 count permitting treatment, 2001-2011, from 200 to 500
 - San Francisco , then New York City begin “test and treat” programs before guidelines issued

2013: All pieces available to include control at source in prevention

- Presidential Executive Order on HIV Continuum of Care, July 15, 2013
 - <http://www.whitehouse.gov/the-press-office/2013/07/15/executive-order-hiv-care-continuum-initiative>
- Public health agencies now know who is infected
- Partner services and linkage to care encouraged by care & prevention funding
 - Not yet routinely related to surveillance, and often unfunded at local level
 - 2012-13 survey (Beyond AIDS): spotty availability of partner services in California public health jurisdictions

2013: All pieces available , contd.

- Treatment can be offered immediately, for patient benefit and to reduce transmission
 - Not yet universally adopted by providers or patients
 - Most countries have not yet accepted immediate treatment
 - Incorporation of prevention into care also essential
- 2014 will be a year of preparation for re-issuance of National HIV/AIDS Strategy in 2015

Classifying prevention methods

- Requires precise definition of exposure
 - In following table, exposure will mean engaging in sexual behavior that could transmit HIV, or in injection drug use
- Alternative definitions for exposure could require that the person be in actual contact with sexual fluids or blood of an infected person
 - Would alter classification of various methods
 - Problematic in that viral load of partner, and use of barriers which exist for sex but not for needle sharing, could complicate definitions
 - Concept of exposure is simpler for smoking, but packs/day still relevant

CLASSIFICATION OF HIV PREVENTION METHODS

METHOD	PREVENTS EXPOSURE?	MITIGATES EXPOSURE?	POPULATION-DIRECTED?	CONTROL AT SOURCE?
1. Screening	Yes only if uninfected reduce exposure risk	Yes if positives reduce risk, start meds	Yes	Yes when test past and current partners
2. Condoms	No	Yes	Yes	Yes when pt./partners use
3. Needle exchange	No	Yes	Yes	Yes when pt. never shares
4. Sexual abstinence and “be faithful” programs (A & B of ABC program in Uganda)	Yes	No	Yes	Yes if pt. abstains or restricts partners
5. HIV education	Yes if leads to reduced exposure risk	Yes if leads to more harm reduction	Yes	Yes when pt./partners get education
6. Drug abuse abstinence and treatment	Yes	No	Yes	Yes if pt. is treated
7. Circumcision	No	Yes	Yes	No

CLASSIFICATION OF HIV PREVENTION METHODS

METHOD	PREVENTS EXPOSURE?	MITIGATES EXPOSURE?	POPULATION-DIRECTED?	CONTROL AT SOURCE?
8. Sero-sorting (positives only have sex with known positives)	No	Yes	Yes for highly exposed ppn.	Yes
9. STD screening and treatment	No	Yes	Yes	Yes, per CDC
10. Antiretroviral treatment of pt. (with virological control)	No	Yes	No	Yes
11. Incorporating prevention into treatment	Yes if leads to abstinence	Yes	No	Yes
12. Partner services	No	Yes, if partner not yet infected	No	Yes
13. Infection control precautions	No	Yes	Yes for occupational ppn.	Yes

CLASSIFICATION OF HIV PREVENTION METHODS

METHOD	PREVENTS EXPOSURE?	MITIGATES EXPOSURE?	POPULATION-DIRECTED?	CONTROL AT SOURCE?
14. PrEP (Pre-exposure prophylaxis)	No	Yes	Yes	No
15. Intra-exposure prophylaxis (including treatment of both infected patient and partner[s], a strategy pending study)	No	Yes	No	Possibly for neg. partner(s) if pt. refuses Tx or condoms or stops latter to cause pregnancy, or if used pending VL reduction
16. Perinatal treatment, mother and newborn	No	Yes	No	Yes
POTENTIAL METHODS				
17. Vaginal microbicide	No	Yes	Yes	Yes
18. Vaccine	No	Yes	Yes	Yes for neg. partners

The viral reproductive ratio, R_0

- R_0 is the number of new cases that result during an initial cases's period of infection (which for HIV is lifetime)
 - If $R_0=1$, disease is stable; if >1 , disease prevalence increases (exponentially at first, till susceptibles exhausted)
- To reduce HIV in population, **R_0 must be <1**
 - Average case must be detected before any transmission, then transmission must be reduced to below replacement levels (<1 new case per existing)
 - Control at source offers hope of achieving this

The viral reproductive rate, R_0 contd.

- Originally developed for demographics (1886)
 - Independently studied for malaria (1911,1927)
 - Now widely used for infectious disease (1975+) R_0 is calculated using the formula of Anderson and May: $R_0 = \beta c D$, where
 - β = transmission probability
 - c = number of contacts
 - D = average time spent infectious (= $1/b$ if the infection rate is b)
 - Can also be thought of as new infections caused by each current infected source person
 - Infections/contact * contacts/time * time/source

Population-directed prevention could be more effective than currently in US

- Uganda experienced dramatic success with “A-B-C” program, late 1980s/early 1990s

(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1544373/>)

- “A” for abstinence (later onset of sexual activity)
- “B” for “be faithful” (partner reduction)
- “C” for condoms, believed to have likely been the least important element
 - Rates in Uganda have relapsed, but other countries in Africa now experiencing decreased incidence
- Urban U.S. gay populations adopted condoms for anal intercourse in 1980s
- In both cases, massive cultural shifts occurred in background of massive morbidity and mortality

Best practices for implementing control-at-source strategy

- Earlier identification of infections (before transmission)
 - Testing more partners of infected persons (**including new partners identified over lifetime of patient**)
 - Continual **redirecting of screening** to demographics of recent reported infections
- **Routine** public health outreach to all newly reported case-persons and/or their providers (**funded at local level**)
 - Linkage to **immediate** & effective treatment
 - Referrals to other services (medical coverage, ADAP, housing, groups)
 - **Initial partner services**

Best practices for implementing control-at-source strategy, contd.

- Incorporation of prevention into ongoing care of patients with HIV, including:
 - Routine, ongoing behavioral/risk reduction counseling
 - Even without this, persons testing (+) tend to reduce risk
 - **Monitoring of treatment adherence**
 - **Monitoring of viral load suppression; call-back of patients**
 - **Ongoing conversation about new partners** to assure partner notification, testing, and linkage (if needed) to treatment
 - Screening for STDs
- *(Highlights above represent opportunities for improvement over current standard of practice in many locations)*

Ultimate potential of this strategy

- U.S. has stabilized but not reduced HIV incidence
 - Using current combination of population-directed prevention and 25% suppression of viral load
 - Incidence rates have been decreasing for drug users, and slightly for heterosexuals, but increasing for gay males
- In countries like U.S. that can afford treatment for all, treatment as prevention offers greatest hope of reduction, if:
 - Increase virologically controlled percentage
 - Achieve control before most transmission occurs
- U.S. could achieve a “generation without AIDS” (Obama State of Union) but not a generation without HIV
 - Successive generations could have lower prevalence of HIV

Only 25% of infected persons in U.S. currently virologically controlled

Study based on National HIV Surveillance system

(Hall, 1 7/27/12 using 2009 data)

- 83% of est. 1.15 million infected persons in U.S. had been tested
- 66% were linked to care (lower if black, young)
- Only 33% had received ART (1/2 of those in care)
- Only 25% had very low viral loads (VL, copies of virus per ml) (3/4 of those receiving ART)
- CDC did own study, 2011, found similar results: 28% controlled

(<http://blog.aids.gov/2012/07/hivaids-treatment-cascade-helps-identify-gaps-in-care-retention.html>)

- Progressing through these steps was called the HIV/AIDS treatment cascade (Gardner), since renamed the “HIV Continuum of Care”

(<http://cid.oxfordjournals.org/content/52/6/793.short?rss=1>;

<http://blog.aids.gov/2012/07/hivaids-treatment-cascade-helps-identify-gaps-in-care-retention.html>)

Theoretical achievable reduction in U.S. HIV incidence using strategy

- Percentage of infected persons tested and knowing diagnosis could be increased about 15%, from 83% to 95% of total
 - Testing could also be redirected toward those most recently infected, prior to most transmission
- 95% of the 95% knowing diagnosis could be linked to care, increasing care by 36%, from 66% to 90% of total
- 95% of the 90% in care could get ART, increasing treatment 58%, from 33% to 85% of total
 - Simply offering treatment to those already linked to care, if 95% accepted, could theoretically treat another 360,000 patients already in care and control viral load in $\frac{3}{4}$ of them (270,000 or 24% of all infected, almost doubling current number controlled)

Theoretical achievable reduction in U.S. HIV incidence using strategy, contd.

- Virological control rate could be increased from 75% to 80% of those treated, by increasing adherence, adjusting meds
- Combining all of the above steps, patients who are almost non-infectious could be increased x2.76, from 25% to about 69% of total ($.95 \times .95 \times .95 \times .80 = .686$)
- 44% more of infected persons (69%-25%) would be only 4% as likely to transmit HIV, once VL controlled
 - **A theoretical potential of 42% decrease in national HIV incidence compared with current...just to start**
 - **With $R_0 < 1$, steady exponential reduction in incidence rates can be maintained over long term**
 - Actual incidence reduction may vary, depending on how much of lifetime transmission has occurred prior to testing; prevalence depends on life expectancy
 - **No other enhancement of prevention is likely to match this**

Antiretroviral prophylaxis: a defining moment in HIV control

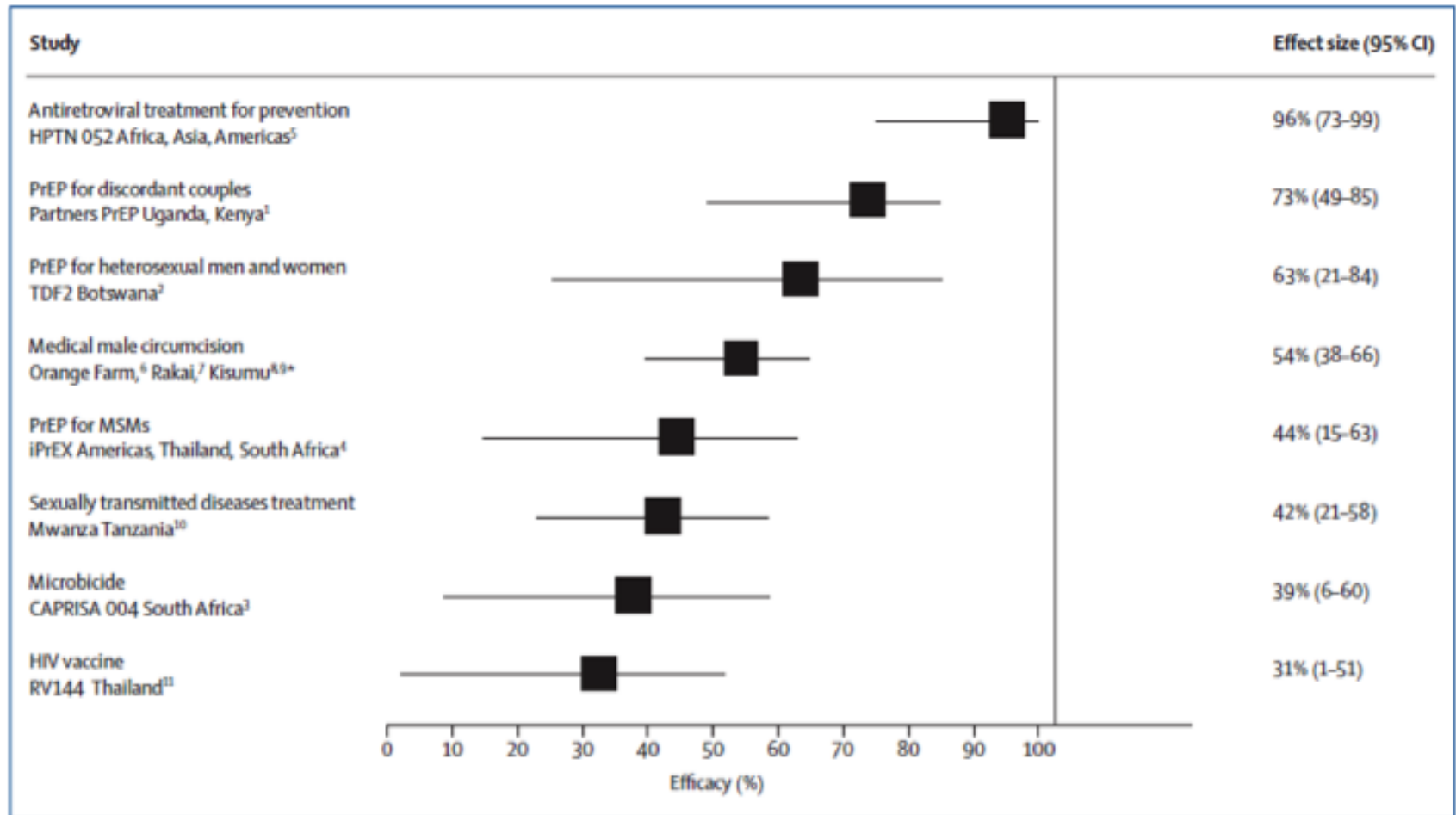


Figure: HIV prevention technologies shown to be effective in reducing HIV incidence in randomised controlled trials¹⁻¹¹

PrEP=Pre-exposure prophylaxis. * Meta-analysis of circumcision trials.

The background of the cover is a high-magnification electron micrograph showing a textured, reddish-purple surface, likely a cell membrane. Numerous small, bright blue spherical particles are scattered across the surface, some appearing to be attached to the membrane and others floating nearby.

Science

23 December 2011 | \$10

BREAKTHROUGH OF THE YEAR

HIV Treatment as Prevention

 AAAS

Effectiveness of combinations of prevention methods

- When methods are combined, rates of remaining infections in a set of interventions can be multiplied together to determine effect on new infections
 - Theoretical example: method A (teen abstinence program) reduces exposures and thus infections by 10%; method B (having 30% of sexually active teens use condoms at 90% effectiveness) by 27%; and method C (getting 50% of the infected potential partners virally suppressed and 96% less infectious) by 48%
 - Remaining infections = $(1-.1)*(1-.27)*(1-.48)$ or $.90*.73*.52=34\%$ of baseline, a decrease of 66%

Effectiveness of combinations of prevention methods, contd.

- Now let's propose further interventions to better those results
 - An additional 10% of teens, or 20%, can be encouraged to be abstinent; 70% of teens will use condoms at 90% effectiveness for 63% reduction; and 75% of infected potential partners can be virally suppressed by 96% for .72 reduction in infectiousness
 - Remaining infections will now be $.80 * .37 * .28 = 8\%$ of baseline
 - This eliminates an additional 26% of baseline infections remaining after the first set of interventions , and is over a 76% improvement over first set (34% down to 8%).

Cost-effectiveness

- In the previous example, three different types of interventions were used, each at two levels of effectiveness
- The key to cost-effectiveness is assessing “bang for the buck”
 - Some interventions will be less expensive than others
 - **Factors include cost per person x size of target population**
 - Increased effort to squeeze out better results from an existing method encounters diminishing returns
 - Adding an additional method may eventually be more cost-effective

Cost-effectiveness of control at source

- The infected person: that's where the virus is
 - The Willy Sutton principle: robbed banks because “that's where the money is”
- Infected persons are a smaller population, and a captive one if in care and/or group programs
- Every prevention adopted by the infected person and partners actually helps reduce HIV transmission
 - By contrast, in a general population, abstinence, condoms, PrEP, etc. adopted by most people do not actually prevent HIV because no active exposure
- Treatment as prevention is expensive, however historically, funding treatment has been achievable

What should public health and medical advocacy groups do?

- Support and advocate for a balanced strategy employing combinations of multiple methods of preventing new infections, to reduce both exposure and harm resulting from exposure
- Emphasize in recommended strategies those that control infection at the source, in appropriate balance with those that target entire at-risk populations
 - Include a major role for treatment as prevention
 - Support funding for routine public health outreach to infected persons and partners, for partner services and linkage to care
- Meet with federal and state public agencies to promote the above and its dissemination to providers, patients, public
- Survey current practices to identify gaps in services
- Recommend further cost-effectiveness studies
 - Support the most cost-effective combinations of population-directed strategies, with control-at-source efforts for patients and partners

What should federal agencies be encouraged to do?

- HHS Headquarters/ONAP: Update National HIV/AIDS Strategy (NHAS)
 - Update due 2015, should stress continuum of care
- HRSA: Widely publicize new treatment guidelines (treat all HIV) to providers, patients, public
- CDC: Update prevention grants to require:
 - Frequent adjustment of demographic targeting of screening and other population-directed programs
 - Outreach to reported cases for linkage to care and partner services; assure these services available at local level nationwide