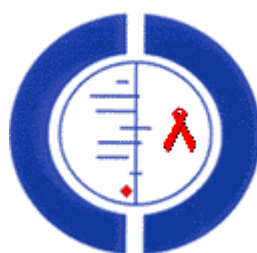


Evidence Assessment:

Strategies for HIV/AIDS Prevention, Treatment and Care



The Cochrane Collaborative Review Group on HIV Infection and AIDS
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SEXUAL TRANSMISSION of HIV

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PARENTERAL TRANSMISSION of HIV

Effective HIV prevention interventions among injection drug users include peer outreach, methadone maintenance and needle exchange programs. Effective interventions to decrease HIV transmission among health care workers and the general community include routine HIV antibody screening, and interventions aimed at improving compliance with universal precautions, as well as promoting the safe and appropriate use of injections and strengthening the quality of blood for transfusions.

PERINATAL TRANSMISSION of HIV

The intervention that appears best suited to prevent mother to child transmission (MTCT) of HIV in resource-poor settings is short course treatment with nevirapine during the mother’s pregnancy. While elective Caesarean delivery and breastmilk replacement seems to be effective in developed countries, more research must be done to determine whether these interventions are appropriate in resource-poor societies.

TREATMENT of HIV, PREVENTION and TREATMENT of OPPORTUNISTIC INFECTIONS (OIs), and PALLIATIVE CARE

The recommended antiretroviral therapy regimen for initial therapy in patients infected with HIV-1 is lamivudine + (zidovudine or stavudine) + (efavirenz or nevirapine). This allows potentially 4 different regimens, which can be tailored for side effects, toxicities, or conditions such as pregnancy or psychiatric illness. Effective medicines are available to prevent and treat OIs. A treatment is available to reduce the risk of active tuberculosis in HIV positive individuals with a positive tuberculin skin test. For those who develop pulmonary tuberculosis, directly observed therapy is effective in helping patients to complete their treatment. There are promising interventions to promote a better quality of life for people living with HIV and AIDS, though additional rigorous research is needed, especially in resource-constrained settings.

Evidence Assessment: Strategies for HIV/AIDS Prevention, Treatment and Care

I. Introduction

The present assessment of the evidence for HIV/AIDS interventions was prepared by staff in the editorial base of the Cochrane Collaborative Review Group on HIV Infection and AIDS,¹ located at the University of California, San Francisco's Institute for Global Health (IGH). George W. Rutherford, MD, is Coordinating Editor of the HIV/AIDS Group (as well as Director of IGH); Gail E. Kennedy, MPH, is the Review Group's Managing Editor. Working closely with Dr. Rutherford, Ms. Kennedy conducted the research for this report, assisted by Tara Horváth, MA, Anne Sunderland, Oliver Bacon, MD, Blair Palmer, MPH, and Lynae Darbes, PhD. The field of HIV/AIDS is evolving very rapidly, and this assessment looked at research available as of the end of December, 2003. This document should be considered a work in progress.

II. Methodology

In order to summarize the evidence of effectiveness of interventions targeting HIV prevention, treatment and care, we conducted a review of high-quality systematic reviews in those topic areas. Robust systematic reviews are a valuable source of information because by locating, appraising and synthesizing evidence from primary studies, they provide empirical answers to focused questions about health issues.² We searched for systematic reviews and meta-analyses of high methodological quality, which met pre-determined criteria of methodologic rigor. Our strong preference was for reviews produced by the Cochrane Collaboration, as Cochrane Reviews³ are recognized as the "gold standard" of such study synthesis. We also searched the Database of Reviews of Effectiveness (DARE), which include only reviews that meet core quality criteria.⁴ Finally, we conducted a PubMed search for interventions in which we found no Cochrane or DARE review, using the "Meta-Analysis" and "Review" filters, and assessed the quality of reviews by pre-determined quality criteria. If more than one review was found which met our criteria, we included the more recent review. We identified more than 60 reviews that met our inclusion criteria.

Assessing the "strength of the evidence" is a difficult task, and many scales and grading systems exist. Since we are attempting only include results from higher methodological quality reviews in our summation of the evidence of effectiveness, we chose only two criteria by which to label the reviews:

Level 1 – Reviews of Randomized Controlled Trials⁵

- A: Met core quality criteria
- B: Did not meet core quality criteria

Level 2 – Reviews of non-experimental studies (observational data)

- A: Met core quality criteria
- B: Did not meet core quality criteria

To summarize the "Level of Effectiveness" for each intervention reviewed, we drew from the "results" and "conclusions" sections of included reviews. We ranked the findings by Level of Effectiveness of the intervention under consideration by the following categories:

- Intervention was found to be **Effective**
- Intervention was found to be **Not Effective**
- Intervention was found to be **Possibly Harmful**
- Unable to assess the level of effectiveness of the intervention because **More Research is Needed** due to lack of high-quality data synthesis or primary research studies.

We summarize our findings in the text grouped by topic area: interventions for sexual HIV transmission; parenteral transmission interventions; mother-to-child transmission interventions; and finally a section focusing on antiretroviral treatments, with prevention and treatment of opportunistic infections, and palliative care for people living with HIV/AIDS. The accompanying Tables, 1-4, correspond to each topic group.

III. Background: HIV/AIDS

The human immunodeficiency virus (HIV) is a human retrovirus that causes Acquired Immune Deficiency Syndrome (AIDS). HIV very likely emerged from two separate primate species in Central and West Africa sometime between 1915-1941.⁶ HIV infects a number of different cells in the body, most importantly two classes of white blood cells called CD4+ lymphocytes and macrophages. These cells ordinarily protect against viral, bacterial, and fungal infections. As the numbers of these cells are depleted, patients become immunodeficient, which in turn leads to infection with opportunistic infections (OIs) such as tuberculosis, bacterial pneumonia, and certain types of cancers.

It is estimated that 95% of all HIV/AIDS cases occur in the developing world. Sub-Saharan Africa is the region most affected. Of the approximately 40 million people living with HIV/AIDS in 2003, more than 25 million were Sub-Saharan Africans (compared to about 1 million North Americans). More than 3 million sub-Saharan Africans were newly infected in 2003, and more than 2 million died of AIDS. The Caribbean and Latin America are the world's worst affected region after Sub-Saharan Africa, with a prevalence of around 2-3%. The epidemic is spreading faster, however, in Eastern Europe and Central Asia than in any other region, with an annual rate of increase of more than 25%. In the year 2003 alone, at least 250,000 people in this region were infected with HIV.⁷

HIV is transmitted by three distinct means:

Sexually:

- Vaginal intercourse
- Anal intercourse
- Oral intercourse

Parenterally (through the skin or veins):

- Blood transfusions
- Sharing of needles and injection equipment for injection drug use (IDU)
- Instruments for scarification and other traditional cutting and piercing practices
- Needlestick injuries (e.g., among health care workers) or unsafe medical injection practices (e.g., re-use of injection needles)

Perinatally (mother-to-child):

- During pregnancy
- During labor and delivery
- Through breast milk

Heterosexual intercourse is by far the most prevalent mode of transmission in Africa and, indeed, in the World. Parenteral transmission through IDU is the most prevalent mode in Eastern Europe and Central Asia, while in East Asia a combination of IDU, heterosexual sex and, to a lesser extent, sex between men, fuel the epidemic. In the Caribbean and Latin America the epidemic is quite diverse; it is driven primarily by heterosexual sex in the Caribbean islands and along the Caribbean coastlines of Central America, while in other parts of the region it spreads primarily through sex between men, and through IDU.⁸

IV. High-risk behaviors and circumstances that heighten the risk of HIV transmission

Risk of acquiring HIV infection involves both the risk of being exposed to an infected person (e.g. the risk of picking an HIV-infected sexual partner), and a variety of biological and cultural factors that increase risk of transmission if exposure occurs. Prevention research has focused both on decreasing risk of exposure (e.g. reducing numbers of sexual partners) and on decreasing risk of transmission if exposure does occur (e.g., using condoms, using antiretroviral drugs, and, in the case of injection drug users, using new or sterilized injection equipment). Research has sought to elucidate which specific interventions prevent transmission amongst people at different levels of risk for infection, since the factors and circumstances contributing to transmission can vary widely.

Prevention efforts may focus on the provision of supplies and services, such as the distribution of condoms and sterilized injection equipment; voluntary counseling and testing (VCT), and improved management of sexually transmitted infections (STIs), among other approaches. These have frequently been combined with educational efforts that aim to reduce high-risk behaviors (for example, peer-led education among female sex workers).

Female sex workers (FSWs) and their clients, STI patients, IDUs, and serodiscordant couples (i.e., couples in which one partner is HIV-positive, and the other is HIV-negative) are among those groups that have been identified as engaging in behavior that places them at-greater risk for HIV infection. Men who have sex with men (MSM) who engage in such behaviors as anal sex with an HIV-positive partner, while not using a condom, are also at increased risk for HIV infection.

Behavior is not the only factor that increases infection risk. Babies born to HIV-infected mothers are at greater risk of infection, as are health care workers (HCW) who may sustain “needlestick” injuries (accidental contact with a used injection needle). In hospitals where the quality of the blood supply may be questionable, members of the general community may be at higher risk, if it is necessary to receive a blood transfusion.

SEXUAL TRANSMISSION of HIV

Male condoms are effective in preventing sexual transmission of HIV. “Targeted” male condom-promotion interventions increase condom use and are the cornerstone of HIV prevention. When combined with one or more of several other interventions, male condom distribution is particularly successful in reducing behavior that places individuals at risk of being infected with HIV. Programs promoting abstinence were found to be ineffective at increasing abstinent behavior and were possibly harmful; more rigorous research is needed to determine the effectiveness of abstinence programs on HIV risk.

V. Interventions for Preventing Sexual Transmission of HIV (see Table 1)

1. Preventing sexual transmission in individuals whose behavior places them at high risk of infection: EFFECTIVE INTERVENTIONS

Sexual transmission of HIV is the most common way in which HIV is transmitted. Sexual transmission includes both heterosexual and homosexual intercourse, and other kinds of sexual contact between individuals. Efforts to decrease the rate of sexual transmission must target heterosexual men and women as well as men-who-have-sex-with-men (MSM). Effective HIV prevention must also address individuals who engage in high-risk behavior, as well as, in the case of generalized epidemics, implement interventions that target the general community.

Male latex condoms, when used consistently and correctly, are highly effective in preventing sexual transmission of HIV.⁹ “Targeted” male condom promotion interventions increase condom use and are the cornerstone of HIV prevention. For example, the distribution of male condoms to high-risk individuals is a vital component of many effective HIV prevention strategies. Male condom distribution coupled with any one of the additional types of interventions listed below has been shown successful in reducing risk behavior among individuals whose behavior places them at high risk. These interventions include:

- Male condom distribution with peer-led education on safe sex behaviors for FSWs.¹⁰
- Male condom distribution with peer outreach and treatment of STIs for FSWs.¹¹
- Male condom distribution for clients of FSWs, particularly men in occupations involving long absences for steady partners, such as truck drivers, factory workers and military.¹²

Other interventions that have proven effective for high-risk individuals include:

- HIV prevention programs aimed at men who engage in behaviors that may increase their risk for HIV infection. Effective interventions are gender specific, focus on relationship and negotiation skills, and involve multiple, sustained contacts, or are community-based.¹³
- Community-based interventions that have the capacity to reach MSM who would not participate in facility-based interventions, who may be at higher risk than many who enroll in small group or individual interventions.¹⁴
- HIV voluntary counseling and testing is an effective secondary prevention strategy when offered to HIV-positive individuals and discordant couples (those in which only one partner is HIV-positive). Counseling following a positive HIV test shows a reduction in unprotected

intercourse and an increase in condom use when HIV-positive individuals learned their HIV status, thereby protecting their sexual partners from becoming infected.¹⁵

- Offering a patient the choice of patient or provider notification to the sexual partners of persons infected with HIV about their exposure to infection (partner notification) as well as health education and counseling. This increases the percentage of partners who will then visit a health care facility. Additional research is needed, however, about the potential risks of domestic violence associated with partner notification.¹⁶

2. Preventing sexual transmission in the general community: EFFECTIVE INTERVENTIONS

Among the general community (i.e., individuals who do not participate in certain behaviors that greatly heighten the risk of infection), several HIV prevention strategies have been shown to be effective:

- Mass media campaigns directed at the distribution and promotion of condoms, combined with comprehensive HIV/AIDS education.¹⁷
- Improving the management and treatment of bacterial sexually transmitted infections STIs in communities with an emerging HIV epidemic (low and slowly rising prevalence), where STI treatment services are poor and where bacterial STIs are highly prevalent.¹⁸
- Behavioral interventions (e.g., skills training) aimed at heterosexual adults are effective in increasing safer sex behaviors, particularly increased use of condoms.¹⁹
- Peer-led behavioral interventions among women that are delivered in multiple sessions are effective in promoting the adoption of condom use.²⁰
- Community level interventions involving peers and popular opinion leaders can be effective in influencing the sexual risk behaviors of MSM.²¹
- Interventions for MSM are more likely to be effective if they are targeted and tailored to a specific community and address the culture with which the men identify (e.g., distinct interventions for men who do and who do not identify as “gay” or “bisexual”).²²
- Both small group interventions and community-level interventions addressing behavior change, risk reduction, negotiation and skills training among MSM are effective in reducing unprotected anal sex.²³
- Interventions targeting MSM of color in the US that were grounded in theory, provided the participants with skills training, and were culturally sensitive to the unique needs of the MSM of color were successful in increasing condom use, decreasing the number of sexual partners, and increasing self-efficacy for protective behavior. All of these outcomes are associated with decreasing HIV infection.²⁴
- Behavioral and social interventions on sexual risk of HIV among sexually experienced adolescents in the US are effective at decreasing sex without condoms and lowering behavioral risk.²⁵
- Effective school-based programs for youth focus on reducing risk-taking behaviors, are theory-based, provide basic accurate information about risks, include activities that address social and media influences, reinforce clear and appropriate individual values and group norms against unprotected sex, and provide modeling and practice in communication and negotiation skills.²⁶

- Theory-based interventions which provide condoms, information and skills building for using condoms and are delivered by a trained facilitator are effective in reducing primary STI infection in adolescents.²⁷

3. Interrupting heterosexual transmission in the general population: INEFFECTIVE INTERVENTIONS

- There is no evidence for benefit from mass STI treatment of communities from the regimen tested in Rakai, Uganda, or from the combined behavioral and improved STI service intervention tested in Masaka (both areas in Uganda where the epidemic has spread into the general population).²⁸

4. Interrupting sexual transmission in general population: POSSIBLY HARMFUL

- There is no evidence that Nonoxynol-9 (N-9) microbicide protects against vaginal acquisition of HIV infection by women from men and, in fact, there is evidence that it may do harm by increasing the frequency of genital lesions which may increase the risk of HIV infection.²⁹
- There are not yet data available for directly assessing the evidence of interventions aimed at delaying sexual intercourse to reduce HIV infection in adolescents. We chose, therefore, to use the proxy of unintended pregnancy outcomes. There is no evidence to support the effectiveness of pregnancy prevention programs aimed at delaying sexual intercourse, improving use of birth control, and reducing incidence of unintended pregnancy in adolescents. An evaluation of four abstinence programs and one school-based sex education program showed an increase in pregnancies of partners of male participants.³⁰ There seems to be little impact on abstinent behavior with sex education programs (both comprehensive sex education and abstinence-oriented programs). Findings show a very weak effect in increasing abstinent behavior with parental involvement, but rigorous studies are lacking at this time to better understand the reasoning for this. More rigorous research is needed.³¹

5. Interrupting sexual transmission: MORE RESEARCH NEEDED

- Only limited and less rigorous research is available for reducing HIV transmission among heterosexual men. High-quality research of social and behavioral interventions that promote heterosexual men's sexual and reproductive health and reduce HIV transmission is needed.³²
- Further research is needed for workplace peer education aimed at male clients of FSWs, especially those working in occupations involving long absences for steady partners (e.g., truck drivers, migrant workers, etc.).³³
- More research is needed on interventions such as VCT, and STI treatment specifically targeted to MSM.³⁴
- Specific interventions are needed to address the particular concerns that MSM may have, e.g. homophobia, and other cultural conditions specific to different communities, that may inhibit MSM from being reached by current prevention efforts.³⁵
- The results from existing observational studies show a strong epidemiological association between male circumcision and prevention of HIV, especially among individuals that engage in risk behavior for HIV, yet insufficient evidence is available at this time to support an interventional effect of male circumcision on HIV acquisition in heterosexual men. The

results of larger randomized trials (presently underway) will need to be carefully considered before circumcision is implemented as a public health intervention for prevention of sexually transmitted HIV.³⁶

- There is a need to assess the acceptability of various partner notification strategies to HIV infected index patients and their partners, especially the potential harms that may occur in societies with stigma associated with being HIV-positive.³⁷
- More rigorous research is needed to assess the effectiveness of on sex education programs (both comprehensive sex education and abstinence-oriented programs).³⁸
- Interventions aimed at preventing HIV in young people such as expanding educational opportunities, especially for young women who are particularly vulnerable to HIV infection, are needed. Evaluations of interventions aimed at street youth and school drop-outs, who engage in high levels of risk behavior, are also needed.³⁹
- More rigorous evaluation of community-wide risk-reduction interventions (e.g., providing HIV education and promoting condom use) are needed.⁴⁰
- There is a need for more evaluation of condom social marketing campaigns.⁴¹
- Further evaluation of the effectiveness and acceptability of female condoms for FSWs is needed.⁴²
- Female-controlled techniques such as vaginal and rectal microbicides (other than N-9), female condoms, and diaphragms need to be investigated further.⁴³
- The suppression of Herpes Simplex Virus Type 2 (HSV 2, genital herpes) as a potential strategy for decreasing HIV transmission in the general population needs further research, since HIV seems to be transmitted more easily during flare-ups of this condition.⁴⁴
- Better evaluations of structural interventions (e.g., the 100% condom use policy in Thailand) and more effort to identify policies that have facilitated HIV prevention in varying contextual situations are needed.⁴⁵
- Research about environmental interventions such as policies that allow spouses and families to move with migrant laborers is needed.⁴⁶
- The effect of using highly active antiretroviral therapy (HAART) as a prevention strategy is unclear at this time and needs to be investigated. Trials suggest that HAART reduces viral load, therefore probably reducing transmissibility. However, the current recommendation of late entry to HAART may mean that no risk reduction occurs. There is also the concern that with HAART accessible to more people, there may be an increase in risky sexual behaviors.⁴⁷
- The use of post-exposure antiretroviral therapy for rape survivors when the serostatus of the rapist is not known needs to be investigated.⁴⁸
- Further study is needed to investigate the effectiveness of the use of post-exposure antiretroviral therapy for the potential HIV exposure in sexual partners of HIV-positive individuals, or individuals who engage in high-risk behavior when serostatus is unknown.⁴⁹
- Interventions that enhance women's economic status, thereby decreasing their vulnerability for HIV infection, need further investigation. Studies are needed to identify ways to improve young women's choices that may decrease the reliance on 'exchange relationships' in which young women have sex with older men in exchange for cash or gifts. Strategies may include income-generating opportunities for women and changes in policy to provide women equal rights in areas including property, inheritance, and divorce, and ensure women access to legal assistance.⁵⁰
- Additional research is needed to determine effective interventions to decrease the stigma that in many cultures adheres to people living with HIV and AIDS. This is important not

only for the quality of life for those living with HIV but may be helpful in preventing further HIV transmission.⁵¹

- There is a need for more research on strategies to reduce sexual violence and coerced sex, especially aimed towards women. Potential strategies include improving the ability of law enforcement to prevent and prosecute violence against women, as well as providing economic and emotional support for survivors of domestic violence.⁵²
- Improved strategies to decrease sex trafficking, e.g. increasing law enforcement efforts, and vigorous prosecution of those involved in business of sex trafficking.⁵³
- Interventions targeting orphans and other vulnerable children who are at increased risk of being infected with HIV through sexual abuse are desperately needed.⁵⁴
- There is a need to assess the impact of offering assistance with school fees, which would enable children to stay in school, thus expanding their options and giving them the benefits of any HIV/AIDS education that is offered.⁵⁵

PARENTERAL TRANSMISSION of HIV

Effective HIV prevention interventions among injection drug users include peer outreach, methadone maintenance and needle exchange programs. Effective interventions to decrease HIV transmission among health care workers and the general community include routine HIV antibody screening, and interventions aimed at improving compliance with universal precautions, as well as promoting the safe and appropriate use of injections and strengthening the quality of blood for transfusions.

VI. Interventions for Preventing Parenteral Transmission of HIV (see Table 2)

Transmission through blood occurs primarily in injection drug users through sharing needles and other injecting works. Health care workers (HCWs) can be exposed to HIV through needlestick punctures and other exposures to blood and body fluids. The general population can be exposed to HIV through unsafe medical practices (e.g. receiving an injection with a previously-used and unsterilized needle, or receiving a transfusion of inadequately screened blood), and through unsafe cultural practices such as tattooing and scarification.

Universal precautions in health care settings are defined as blood and body fluid precautions to be used consistently for all patients regardless of their bloodborne infection status. Although universal precautions are the standard of practice for preventing HIV transmission among HCWs, interventions are needed to improve compliance with universal compliance in health care settings.

1. Interrupting parenteral transmission in injection drug users (IDUs): EFFECTIVE INTERVENTIONS

Effective HIV prevention strategies for IDUs include:

- Evidence strongly supports the effectiveness of needle exchange programs in reducing HIV incidence amongst IDUs, though they do not decrease drug use.⁵⁶
- Oral substitution treatment (such as methadone) for opioid-dependent injection drug users is associated with reductions in illicit opioid use, injecting use and sharing of injecting equipment. It is also associated with reductions in the proportion of injecting drug users

reporting multiple sex partners or exchanges of sex for drugs or money; these reductions in risk behavior translate to reductions in new HIV infections.⁵⁷

- HIV/AIDS risk-reduction interventions for clients enrolled in drug abuse treatment programs are effective for decreasing sexual risk behavior; improving risk-reduction skills; and decreasing risky injection practices.⁵⁸
- Outreach-based HIV interventions are effective in reaching out-of-treatment IDUs and improve drug and sex risk behaviors, thus decreasing HIV transmission.⁵⁹
- Intensive and sustained peer outreach and behavior change programs focusing on reducing risky drug use and sexual practices show a decrease in risk factors among stable and motivated IDUs though intervention participants continue to engage in a high level of risky behaviors.⁶⁰
- Interventions aimed at drug users (those that use injecting drugs and non-injecting drugs) are effective in reducing unprotected sex and increasing the use of male condoms (based on studies from the US).⁶¹

2. Interrupting parenteral transmission in healthcare workers (HCWs) and the general population: EFFECTIVE INTERVENTIONS

- Improving compliance with universal precautions, making available adequate and accessible barriers (latex and non-latex gloves) to all health care workers and sufficient time for HCWs to use them.⁶²
- The safe and appropriate use of injections, including provision of single-use syringes, training and public education are effective at reducing transmission through unsafe medical injections.⁶³
- Hospital-based routine HIV antibody screening is effective in securing a safe blood supply.⁶⁴
- Strengthening the quality of blood for transfusions through deferring high-risk donors, recruitment of volunteers and non-remunerated donors, and decreasing unnecessary blood transfusions are key to preventing parenteral transmission in the general population.⁶⁵

3. Interrupting parenteral transmission: INEFFECTIVE INTERVENTIONS

- Efforts to stop drug trafficking (and thereby reduce the drug supply) and implement stiffer criminal penalties for drug traffickers and drug users have been shown not to be effective as HIV prevention measures.⁶⁶

4. Interrupting parenteral transmission: MORE RESEARCH NEEDED

- Psychosocial interventions designed to reduce drug use and sexual risk taking of IDUs by changing the norms of entire communities of drug users need to be designed and evaluated.⁶⁷
- Combination antiretroviral therapy used following a needle stick injury (post-exposure prophylaxis, or PEP) in which the HIV status of the blood is unknown and therefore there is a risk of HIV transmission to the health care worker. Although the use of PEP is offered in many healthcare settings in resource-rich areas, more research is needed to determine the effectiveness of the intervention in resource-limited settings and strategies to implement the intervention.⁶⁸

- In cultures where scarification and other traditional practices that cause bleeding are common, interventions to create safer practices are needed.⁶⁹
- Detoxification and drug abstinence programs and the use of traditional healers for treating drug users all need to be further assessed.⁷⁰
- In many areas of the world, the reuse of injection equipment without sterilization is commonly used. Interventions to decrease the overuse of injections and improve the safety of injection practices are needed.⁷¹
- More research of effective strategies to recruit and retain low-risk blood donors is needed.⁷²
- The use of virucidal heat treatment may be effective at viral inactivation of HIV in collected blood. More research is needed.⁷³

PERINATAL TRANSMISSION of HIV

The intervention that appears best suited to prevent mother to child transmission (MTCT) of HIV in resource-poor settings is short course treatment with nevirapine during the mother's pregnancy. While elective Caesarean delivery and breastmilk replacement seems to be effective in developed countries, more research must be done to determine whether these interventions are appropriate in resource-poor societies.

VII. Interventions for Perinatal (Mother-to-Child) Transmission of HIV (see Table 3)

Newborns are exposed to HIV through their HIV-infected mothers during birth (through blood and vaginal secretions) and through breastfeeding. Issues related to the feasibility of interventions in resource poor settings need to be considered such as Caesarean sections and the use of formula feeding rather than breastfeeding. In most cultures breastfeeding is the norm, and HIV infected women, if they do not breastfeed, can be stigmatized as HIV infected in their communities. Thus, it important to address the stigma attached with HIV infection as well as effective intervention strategies to promote safe feeding practices of newborns.

1. Interrupting Perinatal Transmission: EFFECTIVE INTERVENTIONS

- Short-course monotherapy with zidovudine has been shown to be effective for decreasing perinatal HIV transmission but nevirapine is cheaper and is given as a single dose to mothers and babies. It therefore appears to be particularly suitable for use in resource-poor settings. Where breastfeeding is almost universal, nevirapine appears to result in a substantially lower risk of mother-to-child transmission than an intrapartum and postpartum regimen of zidovudine.⁷⁴
- Elective use of Caesarean section versus a vaginal birth for delivery of the newborn has proven effective in reducing perinatal HIV transmission with no serious postpartum complications when tested in developed countries, yet the risk to the mother in resource-poor settings is still uncertain. In the presence of effective antiretroviral therapy, the additional benefit of delivery by elective Caesarean section may be small and offset by an increase in the risk of the procedure for the mother.⁷⁵
- The use of formula feedings rather than breastfeeding has proven effective in limited studies to decrease HIV transmission in infants, yet infants from resource-limited areas that are not

breastfed have a six-fold greater risk of dying from infectious diseases in the first 2 months of life than those who are breastfed.⁷⁶

2. Interrupting Perinatal Transmission: INEFFECTIVE INTERVENTIONS

- Antenatal and intrapartum vitamin A supplementation is not effective in reducing perinatal transmission of HIV and adverse pregnancy outcomes among HIV-infected pregnant women.⁷⁷

3. Interrupting Perinatal Transmission: MORE RESEARCH NEEDED

- Rigorous evaluations of the use of combination antiretroviral therapy in pregnancy are needed. In particular, attempts should be made to limit the exposure of the fetus in utero, either in duration or dose, to drugs of unknown teratogenicity. Ideally, all children born to women receiving combination antiretroviral therapy in pregnancy should be followed up so that evidence of long-term toxicity, if it occurs, can be recognised early.⁷⁸
- The potential value of nevirapine used for longer durations in breastfeeding populations needs to be considered as it may further reduce the risk of mother-to-child transmission.⁷⁹
- Investigating the feasibility of the universal use of nevirapine among all pregnant women in high-prevalence areas needs further investigation.⁸⁰
- Further research is needed on interventions promoting safer breastfeeding which includes exclusive breastfeeding and abrupt weaning in which infants are given nothing but breastmilk for the first 6 months and then are abruptly cut off. (Food and liquid other than breastmilk often given to infants may irritate the linings of the intestines, which may then increase the chances of an infant's body absorbing HIV from breastmilk. Limiting the mixture of table food and breastmilk may be important.)⁸¹
- Other strategies aimed at reducing transmission through breastfeeding need to be further evaluated. These include:
 - Interventions offering support and encouragement of good breast feeding practices (avoiding feeding from breasts with mastitis or abscesses)
 - breast milk pasteurization and pooled, treated breast milk
 - the use of wet-nurses
 - the production of a vaccine-generated immune response in breastfeeding infants⁸²
- Well-designed studies of vaginal disinfection during birth are needed to assess the effectiveness of this intervention on HIV infection rates in newborns.⁸³
- In order to introduce an intervention which is aimed specifically at HIV-infected women, as opposed to interventions (such as vaginal cleansing) which can be used for all pregnant women, it will be necessary to identify those women who are HIV infected before the intervention can be given. If this cannot be achieved, for whatever reason, then even the most effective intervention will not reduce the burden of disease in these populations.⁸⁴
- The effectiveness of elective Caesarean section in women receiving optimal antiretroviral therapy needs further evaluation.⁸⁵

TREATMENT of HIV, PREVENTION and TREATMENT OF OPPORTUNISTIC INFECTIONS (OIs), and PALLIATIVE CARE

The recommended antiretroviral therapy regimen for initial therapy in patients infected with HIV-1 is lamivudine + (zidovudine or stavudine) + (efavirenz or nevirapine). This allows potentially 4 different regimens, which can be tailored for side effects, toxicities, or conditions such as pregnancy or psychiatric illness. Effective medicines are available to prevent and treat OIs. A treatment is available to reduce the risk of active tuberculosis in HIV positive individuals with a positive tuberculin skin test. For those who develop pulmonary tuberculosis, directly observed therapy is effective in helping patients to complete their treatment. There are promising interventions to promote a better quality of life for people living with HIV and AIDS, though additional rigorous research is needed, especially in resource-constrained settings.

VIII. Treatment of HIV, Prevention and Treatment of Opportunistic Infections (OIs), and Palliative Care (see Table 4)

To help tackle the worldwide epidemic, clinical management, pharmaceutical therapy, and prevention of further HIV transmission are needed in a comprehensive approach to caring for HIV-infected individuals. This approach may include, as appropriate, treatment with antiretroviral (ARV) medications, prevention and treatment of opportunistic infections (OIs), and palliative care.

1. Treatment of HIV infection with antiretroviral therapy: EFFECTIVE INTERVENTIONS

Antiretroviral medicines suppress viral replication and improve symptoms. Providing treatment for HIV-infected people is essential to alleviate the suffering and mitigate the devastation associated with the AIDS pandemic. The provision of treatment offers hope to the millions infected with HIV, which will create a demand for testing and counseling to determine HIV status. It also offers a unique opportunity to strengthen HIV prevention efforts by increasing awareness of the disease and offering strategies to reduce transmission as well as reducing the stigma and discrimination associated with HIV.

- Antiretroviral therapy consisting of 3 drugs is more effective in reducing death and disease progression, as well as improving surrogate markers (CD4 count and HIV viral load) than regimens containing 1 or 2 drugs.⁸⁶
- Three-drug regimens containing two NRTIs with a PI, a NNRTI, or a third NRTI may provide comparable effectiveness in antiretroviral-naïve adults and practical issues such as daily pill burden should be considered when choosing a treatment regimen.⁸⁷
- The World Health Organization (WHO) recommends the following 5-drug “formulary approach to initial therapy in patients infected with HIV-1: lamivudine + (zidovudine **or** stavudine) + (efavirenz **or** nevirapine). This allows 4 potential regimens that can be tailored for certain side effects, toxicities, or conditions such as pregnancy or psychiatric illness.⁸⁸
- For treatment failure after starting one of these regimens, the WHO recommends the following formulary-based approach: didanosine + (tenofovir **or** abacavir) + (ritonavir-boosted lopinavir **or** ritonavir-boosted saquinavir, **or** nelfinavir if refrigeration is unavailable).⁸⁹

- For initial treatment of patients infected with HIV-2 or HIV-1 subtype O, viruses which are not susceptible to non-nucleoside reverse transcriptase inhibitors (NNRTIs), the guidelines recommend starting with a protease-inhibitor (PI) based regimen.⁹⁰
- Triple therapy with two NRTIs and one non-NRTI (efavirenz or nevirapine) is more effective than therapy with two NRTIs at reducing viral load in ARV-naïve patients. Treatment with two NRTIs and one non-NRTI yield a slightly better virological response and was better tolerated than two NRTIs and a PI.⁹¹
- PI-sparing HAART consisting of Nevirapine plus 2 NRTIs effectively reduced HIV viral load treatment-naïve patients with either high or low baseline viral loads.⁹²
- When used in combination with zidovudine (AZT), the use of didanosine (ddI) and, to a lesser extent, zalcitabine (ddC) delayed both HIV disease progression and death. The comparative effects of these different nucleoside analogues should inform the choice of triple antiretroviral regimens⁹³
- Although it is desirable to reduce the number of antiretroviral drugs given in combination therapy for reasons of compliance and toxicity, maintenance regimens with fewer drugs (two or less) are associated with significantly increased resistance and risk of loss of viral suppression. Successful initial therapy (of at least three drugs), as evidenced by suppression of viral load, should not be decreased in the maintenance phase unless clinically necessary.⁹⁴
- Evidence demonstrates that a pharmacist-led intervention consisting of educational counseling and availability of follow-up telephone support with conventional dispensing of HAART pills improves adherence to HAART however, this intervention did not improve the percentage of patients with undetectable viral load at 24 weeks.⁹⁵
- HIV RNA and CD4 lymphocyte count correlate with disease progression, and are useful surrogate markers for determining efficacy, in clinical trials of antiretroviral drugs.⁹⁶
- For patients failing ARV therapy, genotypic resistance testing along with expert interpretation of results is effective in improving virologic outcomes.⁹⁷

2. Treatment of HIV infection with antiretroviral therapy: MORE RESEARCH NEEDED

- Controlled trials are urgently needed to determine which interventions can significantly improve adherence to HAART. Whether interventions that improve adherence also suppress viral load and improve clinical outcomes should also be considered.⁹⁸
- Interventions to promote adherence that focus on the provider and the patient-provider relationship, variables related to the treatment regimen or illness and contextual factors are all needed. Also investigations into the timing of when to begin the intervention in patients are needed as well as strategies targeting special groups of patients such as children and drug users.⁹⁹
- Research is needed to determine the efficacy of planned structured treatment interruptions as a way to decrease the drug-taking burden, side effects and costs associated with ARV therapy.¹⁰⁰

3. Prevention and treatment for opportunistic infections: EFFECTIVE INTERVENTIONS

Opportunistic infections are illnesses caused by various organisms, some of which usually do not cause disease in persons with healthy immune systems. Persons living with advanced HIV infection suffer opportunistic infections of the lungs, brain, eyes, and other organs. Opportunistic infections common in persons diagnosed with AIDS include *Pneumocystis carinii* pneumonia (PCP); Kaposi's

sarcoma (KS); cryptosporidiosis; histoplasmosis; other parasitic, viral and fungal infections; and some types of cancers. There are strong concerns over the development of antibiotic-resistant bacterial and fungal infections which will interfere with the ability to effectively prevent and treat OIs, and drive up the associated health care costs.

- Administration of trimethoprim-sulfamethoxazole is effective as a prophylaxis for *P. carinii* pneumonia and toxoplasmosis in HIV-infected patients.¹⁰¹
- Prophylaxis with trimethoprim-sulfamethoxazole (cotrimoxazole, Bactrim, Septra) has a beneficial effect in preventing death and illness episodes due to OIs in adults with both early and advanced HIV disease in western Africa. However, the wider applicability of these findings is unclear, in particular to areas with higher background bacterial resistance to Cotrimoxazole. Further trials are required in differing settings to widen applicability.¹⁰²
- The discontinuation of prophylaxis for PCP is seen as a useful strategy in patients infected with HIV who had adequate immune recovery while receiving highly active antiretroviral therapy.¹⁰³
- Treatment of latent tuberculosis infection (LTBI) with isoniazid taken for six to 12 months is effective in reducing the risk of active tuberculosis in HIV positive individuals with a positive tuberculin skin test.¹⁰⁴
- Directly observed therapy is an effective intervention for assisting HIV-infected patients to complete treatment of pulmonary tuberculosis (TB) though the optimal duration of the treatment is still controversial.¹⁰⁵
- Nystatin, fluconazole, ketoconazole and itraconazole are effective treatments for oral candidiasis.¹⁰⁶
- Although data from randomised controlled trials on effective treatments for HIV associated KS are sparse, particularly among people who are also taking HAART several interventions are effective. Only radiotherapy treatment is a feasible treatment option in resource-poor settings at this time.¹⁰⁷
 - Pegylated liposomal doxorubicin appears to give a superior response rate and cause a similar number of adverse events compared to standard regimens when used among patients with advanced KS.
 - Alitretinoin gel appears effective and safe for use in the treatment of cutaneous KS, among patients with a relatively high performance status.
 - Radiotherapy is effective in treating cutaneous lesions with higher doses being associated with a more prolonged response at the expense of greater toxicity.
- The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for HIV-infected patients with *P. carinii* pneumonia who are unresponsive to conventional antipneumocystis agents.¹⁰⁸

4. Prevention and Treatment for opportunistic infections: MORE RESEARCH NEEDED

- Although cotrimoxazole has been shown to be effective in western Africa, further trials are needed to determine wider applicability of these findings, particularly in areas with higher background bacterial resistance to cotrimoxazole.¹⁰⁹
- The effectiveness of routinely administered cotrimoxazole on death and illness episodes in children with HIV infection, and in infants of HIV infected mothers, needs to be assessed.¹¹⁰

- More research is needed to determine the efficacy of valganciclovir, a new oral agent for the therapy of cytomegalovirus (CMV) retinitis is shown to be effective in the treatment of CMV retinitis in HIV-positive patients, and has easy administration and a lack of potential catheter-related complications.¹¹¹
- Further research is needed to determine if dapsone is effective for use as a secondary PCP prophylaxis.¹¹²
- The majority of treatment options for patients with Kaposi's sarcoma in resource-poor settings are unlikely to be available or affordable in developing countries where the bulk of HIV infection and KS occur, apart from radiotherapy that may be available in a few tertiary centres. Recent changes in pricing mean that HAART is likely to become more available to developing countries in the near future. In this context, trials designed to look at the effect of cheaper and more widely available chemotherapeutic agents for the treatment of HIV associated KS among patients already on HAART are a priority. One such trial is underway in South Africa.¹¹³
- More research is needed to determine the most effective regimen of isoniazid for preventing active TB in HIV-infected patients with latent TB. The choice of regimen will depend on factors such as cost, adverse effects, adherence and drug resistance. In addition, trials evaluating the long-term effects of anti-tuberculosis chemoprophylaxis and the influence of level of immunocompromise on effectiveness are needed.¹¹⁴
- Although standard rifampin containing short-course regimens are very effective in treating pulmonary tuberculosis in healthy immunocompetent people, the optimal duration of therapy for tuberculosis in HIV-infected patients is controversial. Some experts have suggested that all HIV-related tuberculosis should be treated with a longer course of therapy, regardless of evidence of early response to therapy. Further assessment of the optimal therapy duration is needed.¹¹⁵
- More research is needed to determine the efficacy and cost-effectiveness of antifungals for the primary prophylaxis of cryptococcal disease in resource limited settings.¹¹⁶
- Further studies are needed for diagnostic and prognostic tests to be used in resource limited settings such as the development of a rapid, portable CD4 test and surrogate tests for viral load and CD4 count.¹¹⁷
- Research is needed to assess strategies to scale up the implementation of ARV treatment in resource-limited settings in order to guarantee that an infrastructure exists to provide ARVs, as well as support and counseling, to HIV-infected patients. One example is the Mother-to-Child-Transmission Plus initiative, which would use MTCT prevention programs as entry points for the treatment of HIV+ women and their families with ARVs. An evaluation of this approach is needed.¹¹⁸
- Additional strategies to scale up ARV therapy management that need further investigation include: low-cost approaches to CD4 cell count and viral load monitoring, monitoring for treatment failure and drug toxicities as well as strategies to improve the affordability and sustainability of drug financing.¹¹⁹

5. Caring for HIV-infected Patients: Complementary and Palliative Care: EFFECTIVE INTERVENTIONS

Complementary care offers care and support to improve the quality of life for HIV-infected individuals. Complementary treatments are used by the majority of HIV-infected people and complement mainstream medicine by offering alternative approaches not addressed or met in

mainstream medicine. Therapies are sought to relieve symptoms, improve overall health and immune systems and improve quality of life. Palliative care is an approach to life-threatening chronic illnesses, especially at the end of life. Palliative care combines active and compassionate therapies to comfort and support patients and their families who are living with life-ending illness. Palliative care strives to meet physical needs through pain relief and maintaining quality of life while emphasizing the patient's and family's rights to participate in informed discussion and to make choices.

- Evidence demonstrates that performing constant or interval aerobic exercise, or a combination of constant aerobic exercise and progressive resistive exercise for at least 20 minutes three times a week for at least four weeks appears to be safe and may be able to improve cardiopulmonary fitness and psychological well-being for adults living with HIV/AIDS.¹²⁰
- Testosterone therapy may be considered in patients with HIV wasting syndrome to reverse muscle loss, but there is a concern about the adverse metabolic effects of long-term testosterone administration and long-term follow-up for these patients is needed.¹²¹
- Stress management in HIV-infected individuals was found to be beneficial for decreasing anxiety and improving self-esteem and CD4 counts.¹²²
- The use of standard antidepressants (imipramine, fluoxetine, and sertraline) or alternative antidepressants (dextroamphetamine and testosterone replacement therapy) are all effective in the treatment of clinical depression among patients with HIV and since each possesses relatively unique benefits, many valuable treatment options are available to address the individual needs of patients.¹²³

6. Caring for HIV-infected Patients: Complementary and Palliative Care: MORE RESEARCH NEEDED

- Many HIV-infected individuals use complementary medicines for caring for HIV infection (acupuncture, herbal medications, stress reduction and vitamins being the most widely used) yet the benefits and risks need further investigation.¹²⁴
- More high quality research is needed to determine the effectiveness of herbal medications to relieve symptoms such as diarrhea and nausea in HIV-infected individuals.¹²⁵
- Larger, more rigorous studies are needed to determine the effectiveness of different forms of palliative care (such as hospital based vs. home based care, the use of coordinating nurses vs. conventional care).¹²⁶
- Although aerobic exercise interventions were found to be effective, further studies are needed to investigate the effects in people living with HIV/AIDS who are children, teens, or older adults since the studies exclusively considered adults between the ages of 18 and 50 years old. The effects of exercise among females demands further attention as females were largely under-represented in the identified trials.¹²⁷
- Rigorous studies are needed to identify if telling the truth about patients' condition has a positive or negative effect on their psychological distress when receiving palliative care.¹²⁸

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- ¹ The Cochrane Collaboration is an international organization that aims to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. The focus of the HIV/AIDS Group is to conduct systematic reviews of randomized controlled trials and other controlled intervention studies to evaluate the prevention, treatment and rehabilitation of HIV infection and AIDS. For more information, please see <http://www.igh.org/Cochrane/>
- ² Centre for Reviews and Dissemination, University of York, UK
- ³ The Cochrane Library
- ⁴ Centre for Reviews and Dissemination, University of York, UK
- ⁵ Randomised Controlled Trials: a user's guide. Alejandro R. Jadad
- ⁶ Korber B et al. Science. 2000 Jun 9;288(5472):1789-96.
- ⁷ UNAIDS/WHO AIDS Epidemic Update as of December 2003. Accessed at <http://www.unaids.org/en/Resources/Publications/Corporate+publications/aids+epidemic+update+-+december+2003.asp>
- ⁸ Global HIV Prevention Working Group. Access to HIV Prevention: Closing the Gap. Accessed at http://www.kff.org/content/2003/200305/Funding_Report_FINAL.pdf
- ⁹ Centers for Disease Control and Prevention
- ¹⁰ Merson et al
- ¹¹ ibid
- ¹² ibid
- ¹³ Exner et al
- ¹⁴ Kegeles & Hart
- ¹⁵ Weinhardt et al
- ¹⁶ Mathews et al (Cochrane Review)
- ¹⁷ Choi & Coates
- ¹⁸ Rutherford et al (Cochrane Review)
- ¹⁹ Choi & Coates
- ²⁰ Wingood et al
- ²¹ NHS Review of Reviews
- ²² ibid
- ²³ Johnson et al (Cochrane Review)
- ²⁴ Darbes et al
- ²⁵ Mullen et al
- ²⁶ Kirby et al
- ²⁷ Yamada et al
- ²⁸ Rutherford et al (Cochrane Review)
- ²⁹ Wilkinson et al (Cochrane Review)
- ³⁰ DiCenso et al
- ³¹ Silva
- ³² Elwy et al
- ³³ Merson et al
- ³⁴ WHO Commission on Macroeconomics and Health
- ³⁵ Valdiserri et al
- ³⁶ Siegfried et al (Cochrane Review)
- ³⁷ Mathews et al (Cochrane Review)
- ³⁸ Silva
- ³⁹ ibid
- ⁴⁰ Merson et al
- ⁴¹ ibid
- ⁴² Merson et al
- ⁴³ DeCock et al
- ⁴⁴ Rutherford, personal communication, 12/2003
- ⁴⁵ ibid
- ⁴⁶ ibid
- ⁴⁷ WHO Commission on Macroeconomics and Health
- ⁴⁸ Rutherford, personal communication, 12/2003

⁴⁹ Valdiserri et al
⁵⁰ Merson et al; Physicians for Human Rights
⁵¹ UNAIDS Barcelona Report
⁵² Physicians for Human Rights
⁵³ ibid
⁵⁴ ibid
⁵⁵ ibid
⁵⁶ Hurley et al
⁵⁷ Gowing et al (Cochrane Review)
⁵⁸ Prendergast et al
⁵⁹ Coyle et al
⁶⁰ Gibson et al
⁶¹ Semaan et al
⁶² Levin
⁶³ Dziekan
⁶⁴ WHO Commission on Macroeconomics and Health
⁶⁵ ibid
⁶⁶ ibid
⁶⁷ Gibson et al
⁶⁸ Valdiserri et al
⁶⁹ Rutherford, personal communication, 12/2003
⁷⁰ WHO Commission on Macroeconomics and Health
⁷¹ Hutin et al
⁷² WHO Commission on Macroeconomics and Health
⁷³ ibid
⁷⁴ Brocklehurst & Volmink (Cochrane Review)
⁷⁵ Brocklehurst (Cochrane Review)
⁷⁶ WHO Collaborative Study Team
⁷⁷ Shey (Cochrane Review)
⁷⁸ Brocklehurst (Cochrane Review)
⁷⁹ Brocklehurst (Cochrane Review)
⁸⁰ Commission on Macroeconomics and Health
⁸¹ Commission on Macroeconomics and Health
⁸² ibid
⁸³ Shey (Cochrane Review)
⁸⁴ Brocklehurst (Cochrane Review)
⁸⁵ ibid
⁸⁶ Jordan et al
⁸⁷ Bartlett et al
⁸⁸ WHO, Scaling Up ARV (2003)
⁸⁹ ibid
⁹⁰ ibid
⁹¹ Torre et al
⁹² Raffi et al
⁹³ Darbyshire et al (Cochrane Review)
⁹⁴ Rutherford et al (Cochrane Review)
⁹⁵ Haddad et al (Cochrane Review)
⁹⁶ Hill et al
⁹⁷ Torre & Tambini
⁹⁸ Haddad et al (Cochrane Review)
⁹⁹ Simoni et al
¹⁰⁰ Pai N. et al (Cochrane, in peer review)
¹⁰¹ Bucher et al
¹⁰² Grimwade et al¹ (Cochrane Review)
¹⁰³ Trikalinos & Ioannidis

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- ¹⁰⁴ Woldehanna & Volmink (Cochrane Review)
¹⁰⁵ Chaulk et al
¹⁰⁶ Patton et al
¹⁰⁷ Dedicoat (Cochrane Review)
¹⁰⁸ Smego et al
¹⁰⁹ Grimwade et al¹ (Cochrane Review)
¹¹⁰ Grimwade et al² (Cochrane Review)
¹¹¹ Cocohoba & McNicholl
¹¹² Saillour-Glennison et al
¹¹³ Dedicoat (Cochrane Review)
¹¹⁴ Woldehanna et al (Cochrane Review)
¹¹⁵ Pai M. (Cochrane protocol)
¹¹⁶ Chang et al (Cochrane, in progress)
¹¹⁷ Hammer et al
¹¹⁸ Hammer et al
¹¹⁹ ibid
¹²⁰ Nixon et al (Cochrane Review)
¹²¹ Kong & Edmonds
¹²² Ozsoy
¹²³ Wagner et al
¹²⁴ Ozsoy
¹²⁵ Liu et al (Cochrane, in peer review)
¹²⁶ Salisbury et al
¹²⁷ Nixon et al (Cochrane Review)
¹²⁸ Leliopoulo et al

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TABLES 1-4

- T 1: Sexual Transmission**
- T 10: Parenteral Transmission**
- T 14: Perinatal Transmission**
- T 17: Treatment, Prevention & Treatment of OIs, and Care**

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
EFFECTIVE INTERVENTIONS: HIGH-RISK BEHAVIORS					
Female sex workers	Male condom distribution with peer-led education on safe sex behaviors for female sex workers (FSWs)	Merson et al	1-A		
Female sex workers	Male condom distribution with peer outreach and treatment of STIs for FSWs	Merson et al	1-A	\$11-\$17 Creese et al	\$1 Creese et al
Female sex workers	Male condom distribution for clients of FSWs, particularly men in occupations involving long absences for steady partners, such as truck drivers, factory workers and military	Merson et al	1-A		
High-risk behavior men	HIV prevention programs aimed at men who engage in behaviors that may increase their risk for HIV infection. Effective interventions are gender specific, focus on relationship and negotiation skills, and involve multiple, sustained contacts, or are community-based	Exner et al	1-A		
High-risk behavior MSM	Community-based interventions have the capacity to reach MSM who would not participate in facility-based interventions, and who may be at higher risk than many who enroll in small group or individual interventions.	Kegeles & Hart	1-A		
HIV+ individuals, serodiscordant couples	HIV counseling and voluntary testing is an effective secondary prevention strategy when offered to HIV positive individuals and discordant couples (those where only one partner is HIV-infected). Counseling following a positive HIV test shows a reduction in unprotected intercourse and an increase in condom use (which were widely available) when HIV+ individuals learned their HIV status, thereby protecting their sexual partners from becoming infected.	Weinhardt et al	1-A		

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
EFFECTIVE INTERVENTIONS: HIGH-RISK BEHAVIORS, continued					
HIV+ persons and their sexual partners	Offering a patient the choice of patient or provider notification to the sexual partners of persons infected with HIV about their exposure to infection (partner notification) as well as health education and counseling. This increases the percentage of partners who will then visit a health care facility. Additional research is needed, however, about the potential risks of domestic violence associated with partner notification.	Mathews et al (Cochrane)	1-A		
EFFECTIVE INTERVENTIONS: GENERAL POPULATION					
General population	Mass media campaigns directed at the distribution and promotion of condoms, combined with comprehensive HIV/AIDS education, are effective at increasing condom use	Choi & Coates	1-A		
General population	Improving the management and treatment of bacterial STIs in communities with an emerging HIV epidemic (low and slowly rising prevalence), where STI treatment services are poor and where bacterial STIs are highly prevalent.	Rutherford et al (Cochrane)	1-A		
General population	Behavioral interventions (e.g., skills training) aimed at heterosexual adults are effective in increasing safer sex behaviors, particularly increased use of condoms.	Choi & Coates	1-A		
General population	Peer-led behavioral interventions among women that are delivered in multiple sessions are effective in promoting the adoption of condom use.	Wingood et al	1-A		

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
EFFECTIVE INTERVENTIONS: GENERAL POPULATION, continued					
MSM	Community level interventions involving peers and popular opinion leaders can be effective in influencing the sexual risk behaviors of MSM.	NHS Review of Reviews	1-A		
MSM	Interventions for MSM are more likely to be effective if they are targeted and tailored to a specific community and address the culture with which the men identify (e.g. distinct interventions for men who do and who do not identify as “gay” or “bisexual”)	NHS Review of Reviews	1-A		
MSM	Both small group interventions and community-level interventions addressing behavior change, risk reduction, negotiation and skills training among MSM are effective in reducing unprotected anal sex.	Johnson et al (Cochrane)	1-A		
MSM	Interventions targeting MSM of color in the US that were grounded in theory, provided the participants with skills training, and were culturally sensitive to the unique needs of the MSM of color were successful in increasing condom use, decreasing the number of sexual partners, and increasing self-efficacy for protective behavior. All of these outcomes are associated with decreasing HIV infection.	Darbes et al	1-A		
Youth	Behavioral and social interventions on sexual risk of HIV among sexually experienced adolescents in the US are effective at decreasing sex without condoms and lowering behavioral risk	Mullen et al	1-A		

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
EFFECTIVE INTERVENTIONS: GENERAL POPULATION, continued					
Youth	Effective school-based programs for youth focus on reducing risk-taking behaviors, are theory-based, provide basic accurate information about risks, include activities that address social and media influences, reinforce clear and appropriate individual values and group norms against unprotected sex, and provide modeling and practice in communication and negotiation skills.	Kirby et al	2-A		
Youth	Theory-based interventions which provide condoms, information and skills building for using condoms and are delivered by a trained facilitator are effective are reducing primary STD infection in adolescents	Yamada et al	1-A		
INEFFECTIVE INTERVENTIONS					
General population (developing countries)	There is no evidence for benefit from mass STI treatment of communities at least for the regimen tested in Rakai, Uganda or from the combined behavioral and improved STI service intervention tested in Masaka (both areas where the epidemic has spread beyond high risk groups into the more general population).	Rutherford et al (Cochrane)	1-A		
EVIDENCE of POTENTIAL HARM					
Women	There is no evidence that Nonoxynol-9 (N-9) microbicide protects against vaginal acquisition of HIV infection by women from men and, in fact, there is evidence that it may do harm by increasing the frequency of genital lesions which may increase the risk of HIV infection.	Wilkinson et al (Cochrane)	1-A		

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
EVIDENCE of POTENTIAL HARM, continued					
Youth	No data available for directly assessing the evidence of interventions aimed at delaying sexual intercourse to reduce HIV infection in adolescents -- must use the proxy of unintended pregnancy outcomes. There is no evidence to support the effectiveness of pregnancy prevention programs aimed at delaying sexual intercourse, improving use of birth control, and reducing incidence of unintended pregnancy in adolescents.	DiCenso et al	1-A		
MORE RESEARCH NEEDED					
Heterosexual men	Only limited and less rigorous research is available for reducing HIV transmission among heterosexual men. High-quality research of social and behavioral interventions that promote heterosexual men's sexual and reproductive health and reduce HIV transmission is needed.	Elwy et al			
Male clients of FSWs	Further research is needed for workplace peer education aimed at male clients of FSWs, especially those working in occupations involving long absences for steady partners	Merson et al			
MSM	Many more rigorous evaluations of HIV prevention efforts with MSM are needed. These populations are often difficult to reach because of the stigma associated with homosexuality but interventions are needed that address specific cultural contexts and stigma.	Merson et al			

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
MORE RESEARCH NEEDED, continued					
Heterosexual men	The results from existing observational studies show a strong epidemiological association between male circumcision and prevention of HIV, especially among high-risk groups, yet insufficient evidence is available at this time to support an interventional effect of male circumcision on HIV acquisition in heterosexual men. The results of larger randomized trials (presently underway) will need to be carefully considered before circumcision is implemented as a public health intervention for prevention of sexually transmitted HIV.	Siegfried et al (Cochrane)			
HIV+ individuals	There is a need to assess the acceptability of various partner notification strategies to HIV infected index patients and their partners and the potential harms that may occur especially in countries with stigma associated with HIV status.	Mathews et al (Cochrane)			
Community	More rigorous evaluation of community-wide risk-reduction interventions such as providing HIV education and promoting condom use are needed	Merson et al			
Community	Better evaluations of structural interventions (such as the 100% condom use policy in Thailand) are needed and more effort is needed to identify policies that have facilitated HIV prevention in varying contextual situations	Merson et al			
Community	Environmental interventions such as policies that allow spouses and families to move with migrant laborers are needed.	Merson et al			

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
MORE RESEARCH NEEDED, continued					
Youth	Interventions aimed at preventing HIV in young people, especially young women who are particularly vulnerable to infection, such as expanding educational opportunities are needed. Also needed are evaluations of interventions aimed at street youth and school drop-outs, some of the most vulnerable groups.	Merson et al			
Community	There is a need for more evaluation of condom social marketing campaigns	Merson et al			
HIV+ individuals	The effect of using HAART as a prevention strategy is unclear at this time but needs to be investigated. Studies suggest that HAART reduces viral load, therefore probably reducing transmissibility but with the current recommendation of late entry to HAART may mean that no reduction occurs. Also with HAART more available, there may be increases in risky sexual behaviors	CMH, WG 5:2			
Rape survivors	The use of post-exposure antiretroviral therapy for rape survivors when the serostatus of the rapist is not known needs to be investigated.	Rutherford			
Sexual partners of individuals with unknown HIV serostatus	Further study is needed to investigate the effectiveness of the use of post-exposure antiretroviral therapy for the potential HIV exposure in sexual partners of HIV infected individuals or high-risk individuals when serostatus is unknown.	Valdiserri et al			

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
MORE RESEARCH NEEDED, continued					
People infected with genital herpes	The suppression of Herpes Simplex Virus Type 2 (genital herpes) as a potential strategy for decreasing HIV transmission in the general population since HIV seems to be transmitted more easily during flare-ups of this condition.	Barcelona Report			
MSM	More research is needed on interventions such as VCT and STI treatment specifically targeted to MSM.	CMH, WG 5:2			
MSM	Specific interventions are needed to address the myriad concerns that MSM have e.g. homophobia and other cultural conditions specific to different populations that inhibit MSM from being reached.	Valdiserri et al			
FSWs	Female condoms for FSWs	Merson et al			
Women	Female-controlled techniques such as vaginal and rectal microbicides (other than N-9), female condoms, and diaphragms need to be further researched.	DeCock et al			
Women	Approaches that enhance women's economic status, thereby decreasing their vulnerability, need further investigation. Studies are needed to identify ways to improve young women's choices that may decrease the reliance on 'exchange relationships' in which young women have sex with older men in exchange for cash or gifts. Strategies may include improving income generating opportunities for women and legal change to provide women equal rights in areas including property, inheritance, and divorce and ensure women access to legal assistance.	Merson et al PHR			

Sexual Transmission of HIV, TABLE 1

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DISABILITY-ADJUSTED LIFE YEARS (DALY) GAINED</u>
MORE RESEARCH NEEDED, continued					
HIV+ individuals	Additional research is needed to determine effective interventions to decrease the stigma that in many cultures adheres to people living with HIV and AIDS which is important not only for the quality of life for those living with HIV but may be helpful in preventing additional HIV transmission.	Barcelona Report			
Women & girls	There is a need for more research on strategies to reduce sexual violence and coerced sex, especially aimed towards women, including strategies to improve to law enforcement in preventing and prosecuting violence against women, economic and emotional support for survivors of domestic violence.	PHR			
Sex workers	Improved strategies to decrease sex trafficking including increasing law enforcement efforts and prosecution of those involved in business of sex trafficking.	PHR			
Children	Interventions targeting orphans and other vulnerable children who are at increased risk of being infected with HIV are desperately needed.	PHR			
Children	There is a need to assess the impact of offering assistance with school fees which enables children to stay in school, thus expanding their options and exposes them to the benefits of any HIV/AIDS education that is offered.	PHR			

Parenteral Transmission of HIV, TABLE 2

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
EFFECTIVE INTERVENTIONS: INJECTION DRUG USERS (IDUs)					
Injection drug users	Evidence strongly supports the effectiveness of needle exchange programs in reducing HIV incidence amongst IDUs, though they do not decrease drug use.	Hurley et al	2-A		
Injection drug users	Oral substitution treatment (such as methadone) for opioid-dependent injecting drug users is associated with reductions in illicit opioid use, injecting use and sharing of injecting equipment. It is also associated with reductions in the proportion of injecting drug users reporting multiple sex partners or exchanges of sex for drugs or money; these reductions in risk behavior translate to reductions in new HIV infections.	Gowing et al (Cochrane)	1-A		
Injection drug users	HIV/AIDS risk-reduction interventions for clients enrolled in drug abuse treatment programs are effective for decreasing sexual risk behavior; improving risk-reduction skills; and decreasing risky injection practices	Prendergast et al	2-B* <i>*Based on article's abstract summary – unable to review complete article.</i>		
Injection drug users	Outreach-based HIV interventions are effective in reaching out-of-treatment IDUs and improve drug and sex risk behaviors, thus decreasing HIV transmission	Coyle et al	2-A		
Injection drug users	Intensive and sustained peer outreach and behavior change programs focusing on reducing risky drug use and sexual practices show a decrease in risk factors among stable and motivated IDUs though intervention participants continue to engage in a high level of risky behaviors.	Gibson et al	2-A		
Injection and other drug users (US studies)	Interventions aimed at drug users (those that use injecting drugs and non-injecting drugs) are effective in reducing unprotected sex and increasing the use of male condoms	Semaan et al	1-A		

Parenteral Transmission of HIV, TABLE 2

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
EFFECTIVE INTERVENTIONS: HEALTH CARE WORKERS (HCWs) and GENERAL POPULATION					
Health care workers	Improving compliance with universal precautions, making available adequate and accessible barriers (latex and non-latex gloves) to all healthcare workers and sufficient time for HCWs to use them.	Levin	2-A		
Health care workers	The safe and appropriate use of injections, including provision of single-use syringes, training and public education are effective at reducing transmission through unsafe medical injections	Dziekan	1-B	\$102 Dziekan	
General population	Hospital-based routine HIV antibody screening is effective in securing a safe blood supply	CMH WG5:2	2-B	\$18-\$107 Creese et al	\$1-\$5 Creese et al
General population	Strengthening the quality of blood for transfusions through deferring high-risk donors, recruitment of volunteers and non-remunerated donors and decreasing the use of unnecessary blood transfusions are key to preventing parenteral transmission in the general population.	CMH WG5:2	2-B	\$18-\$107 McFarland et al	\$1-\$5 McFarland et al
INEFFECTIVE INTERVENTIONS					
Injection drug users	Efforts to stop drug trafficking (and thereby reduce the drug supply) and implement stiffer criminal penalties for drug traffickers and drug users have been shown not to be effective as HIV prevention measures	CMH WG5:2	2-B		

Parenteral Transmission of HIV, TABLE 2

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
MORE RESEARCH NEEDED					
Injection drug users	Psychosocial interventions designed to reduce drug use and sexual risk taking of IDUs by changing the norms of entire communities of drug users need to be designed and evaluated.	Gibson			
Health care workers	Combination antiretroviral therapy used following a needle stick injury (post-exposure prophylaxis, or PEP) in which the HIV status of the blood is unknown and therefore there is a risk of HIV transmission to the health care worker. Although the use of PEP is offered in many healthcare settings in resource-rich areas, more research is needed to determine the effectiveness of the intervention in resource-limited settings and strategies to implement the intervention.	Valdiserri et al			
General population	In cultures where scarification and other traditional practices that cause bleeding are common, interventions to create safer practices are needed.	Rutherford			
Injection drug users	Detoxification and drug abstinence programs and the use of traditional healers for treating drug users all need to be further assessed.	CMH WG5:2			
Health care workers	In many areas of the world, the reuse of injection equipment without sterilization is commonly used. Interventions to decrease the overuse of injections and improve the safety of injection practices are needed.	Hutin et al			
General population	More research is needed of effective strategies to recruit and retain low-risk blood donors.	CMH WG5:2			

Parenteral Transmission of HIV, TABLE 2

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
MORE RESEARCH NEEDED, continued					
General population	The use of virucidal heat treatment may be effective at viral inactivation of HIV in collected blood.	CMH WG5:2			

Perinatal (Mother-to-Child) Transmission of HIV, TABLE 3

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
EFFECTIVE INTERVENTIONS, HIGH-RISK INDIVIDUALS					
HIV+ pregnant women	Short-course monotherapy with zidovudine has been shown to be effective for decreasing perinatal HIV transmission but nevirapine is cheaper and is given as a single dose to mothers and babies. It therefore appears to be particularly suitable for use in resource-poor settings. Where breastfeeding is almost universal, nevirapine appears to result in a substantially lower risk of mother-to-child transmission than an intrapartum and postpartum regimen of zidovudine	Brocklehurst & Volmink (Cochrane)	1-A	Single dose NVP: \$20-\$341 Marseille et al	Single dose NVP: \$1-\$12 Marseille et al
Infants born to HIV+ women	The use of formula feedings rather than breastfeeding has proven effective in limited studies to decrease HIV transmission in infants yet infants from resource-limited areas that are not breastfed have a six-fold greater risk of dying from infectious diseases in the first 2 months of life than those who are breastfed	WHO Collaborative Study Team	1-A		
HIV+ pregnant women and their infants	Elective use of Cesarean section versus a vaginal birth for delivery of the newborn has proven effective in reducing perinatal HIV transmission with no serious postpartum complications when tested in developed countries, yet the risk to mother in resource poor settings is still uncertain. In the presence of effective antoretroviral therapy, the additional benefit of delivery by elective caesarean section may be small and offset by an increase in the risk of the procedure for the mother.	Brocklehurst (Cochrane)	1-A		
INEFFECTIVE INTERVENTIONS					
HIV+ pregnant women	Antenatal and intrapartum vitamin A supplementation is not effective in reducing perinatal transmission of HIV and adverse pregnancy outcomes among HIV-infected pregnant women.	Shey (Cochrane)	1-A		

Perinatal (Mother-to-Child) Transmission of HIV, TABLE 3

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
MORE RESEARCH NEEDED					
HIV+ pregnant women Infants born to HIV+ women	Rigorous evaluations of the use of combination antiretroviral therapy in pregnancy are needed. In particular, attempts should be made to limit the exposure of the fetus in utero, either in duration or dose, to drugs of unknown teratogenicity. Ideally all children born to women receiving combination antiretroviral therapy in pregnancy should be followed up so that evidence of long term toxicity, if it occurs, can be recognised early.	Brocklehurst (Cochrane)			
HIV+ pregnant women Infants born to HIV+ women	Well-designed studies of vagina disinfection during birth are needed to assess the effectiveness of this intervention on HIV infection rates in newborns.	Shey (Cochrane)			
HIV+ mothers of infants Infants born to HIV+ women	The potential value of nevirapine used for longer durations in breastfeeding populations needs to be considered as it may further reduce the risk of mother-to-child transmission.	Brocklehurst (Cochrane)			
HIV+ mothers of infants Infants born to HIV+ women	Further research is needed on interventions promoting safer breastfeeding which includes exclusive breastfeeding and abrupt weaning in which infants are given nothing but breastmilk for the first 6 months and then are abruptly cut off. (Food and liquid other than breastmilk often given to infants may irritate the linings of the intestines, which may then increase the chances of an infant's body absorbing HIV from breastmilk. Limiting the mixture of table food and breastmilk may be important.)	CMH WG5:2			
HIV+ mothers of infants Infants born to HIV+ women	Other strategies, e.g. offering support and encouragement of good breast feeding practices, breast milk pasteurization and pooled, treated breast milk, the use of wet nurses, and the production of a vaccine-generated immune response in breastfeeding infants.	CMH WG5:2			

Perinatal (Mother-to-Child) Transmission of HIV, TABLE 3

<u>POPULATION</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>COST PER INFECTION AVERTED</u>	<u>DALY GAINED</u>
MORE RESEARCH NEEDED, continued					
HIV+ pregnant women	In order to introduce an intervention which is aimed specifically at HIV infected women, as opposed to interventions (such as vaginal cleansing) which can be used for all pregnant women, it will be necessary to identify those women who are HIV infected before the intervention can be given. If this cannot be achieved, for whatever reason, then even the most effective intervention will not reduce the burden of disease in these populations.	Brocklehurst (Cochrane)			
HIV+ pregnant women	The effectiveness of elective caesarean section in women receiving optimal antiretroviral therapy needs further evaluation.	Brocklehurst (Cochrane)			
HIV+ pregnant women	Investigating the feasibility of the universal use of nevirapine among all pregnant women in high-prevalence areas needs to be studied.	CMH WG5:2			

<u>TREATMENT STRATEGY</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>DALY GAINED</u>
EFFECTIVE INTERVENTIONS				
ARV for HIV infection	When used in combination with zidovudine (AZT), the use of didanosine (ddl) and, to a lesser extent, zalcitabine (ddC) delayed both HIV disease progression and death. The comparative effects of these different nucleoside analogues should inform the choice of triple antiretroviral regimens.	Darbyshire et al (Cochrane)	1-A	
ARV for HIV infection	Antiretroviral therapy consisting of 3 drugs is more effective in reducing death and disease progression, as well as improving surrogate markers (CD4 count and HIV viral load) than regimens containing 1 or 2 drugs.	Jordan et al	1-A	
ARV for HIV infection	Three drug regimens containing two NRTI with a PI, a NNRTI, or a third NRTI may provide comparable effectiveness in antiretroviral-naive adults and practical issues such as daily pill burden should be considered when choosing a treatment regimen.	Bartlett et al	1-A	
ARV for HIV infection	5-drug “formulary approach” to initial therapy in patients infected with HIV-1: lamivudine + (zidovudine or stavudine) + (efavirenz or nevirapine). This allows 4 potential regimens that can be tailored for certain side effects, toxicities, or conditions such as pregnancy or psychiatric illness.	Scaling up ARV (2003)	1-B	
ARV for HIV infection	For treatment failure after starting one of these (above) regimens, the WHO recommends the following formulary-based approach: didanosine + (tenofovir or abacavir) + (ritonavir-boosted lopinavir or ritonavir-boosted saquinavir, or nelfinavir if refrigeration is unavailable).	Scaling up ARV (2003)	1-B	
ARV for HIV infection	For initial treatment of patients infected with HIV-2 or HIV-1 subtype O, viruses which are not susceptible to non-nucleoside reverse transcriptase inhibitors (NNRTIs), the guidelines recommend starting with a protease-inhibitor (PI) based regimen.	Scaling up ARV (2003)	1-B	

<u>TREATMENT STRATEGY</u>	<u>INTERVENTION TYPE</u>	<u>EVIDENCE BASE</u>	<u>STRENGTH of EVIDENCE</u>	<u>DALY GAINED</u>
EFFECTIVE INTERVENTIONS, continued				
ARV for HIV infection	Triple therapy with two NRTIs and one non-NRTI (efavirnz or nevirapine) is more effective than therapy with two NRTIs at reducing viral load in ARV naive patients. Treatment with two NRTIs and one non-NRTI yield a slightly better virological response and was better tolerated than two NRTIs and a PI.	Torre et al	1-B	
ARV for HIV infection	PI-sparing HAART consisting of Nevirapine plus 2 NRTIs effectively reduced HIV viral load treatment-naïve patients with either high or low baseline viral loads.	Raffi et al	1-B	
ARV for HIV infection	HIV RNA and CD4 lymphocyte counter correlate with disease progression, and are useful surrogate markers for determining efficacy, in clinical trials of antiretroviral drugs.	Hill et al	1-B	
ARV for HIV infection	Evidence demonstrates that a pharmacist-led intervention consisting of educational counseling and availability of follow-up telephone support with conventional dispensing of HAART pills improves adherence to HAART. However, this intervention did not improve the percentage of patients with undetectable viral load at 24 weeks.	Haddad et al (Cochrane)	1-A	
ARV for HIV infection	Although it is desirable to reduce the number of antiretroviral drugs given in combination therapy for reasons of compliance and toxicity, maintenance regimens with fewer drugs (two or less) are associated with significantly increased resistance and risk of loss of viral suppression. Successful initial therapy (of at least three drugs), as evidenced by suppression of viral load, should not be decreased in the maintenance phase unless clinically necessary.	Rutherford et al (Cochrane)	1-A	
ARV for HIV infection	For patients failing ARV therapy, genotypic resistance testing along with expert interpretation of results is effective in improving virologic outcomes.	Torre & Tambini	1-B	
Preventing OIs	Administration of trimethoprim-sulfamethoxazole is effective as a prophylaxis for P. carinii pneumonia and toxoplasmosis in HIV-infected patients.	Bucher et al	1-A	

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EFFECTIVE INTERVENTIONS, continued				
Preventing OIs	Prophylaxis with Trimethoprim-Sulfamethoxazole (cotrimoxazole, Bactrim, Septra) has a beneficial effect in preventing death and illness episodes due to OIs in adults with both early and advanced HIV disease in western Africa. However, the wider applicability of these findings is unclear, in particular to areas with higher background bacterial resistance to Cotrimoxazole. Further trials are required in differing settings to widen applicability.	Grimwade et al (Cochrane)	1-A	
Preventing OIs	The discontinuation of prophylaxis for Pneumocystis carinii pneumonia (PCP) is seen as a useful strategy in patients infected with human immunodeficiency virus who had adequate immune recovery while receiving highly active antiretroviral therapy.	Trikalinos & Ioannidis	1-A	
Preventing OIs	Treatment of latent tuberculosis infection (LTBI) with isoniazid taken for six to 12 months is effective in reducing the risk of active tuberculosis in HIV positive individuals with a positive tuberculin skin test.	Woldehanna et al (Cochrane)	1-A	
Treating OIs	Directly observed therapy is an effective intervention for assisting HIV-infected patients to complete treatment of pulmonary tuberculosis (TB) though the optimal duration of the treatment is still controversial.	Chaulk et al	1-A	
Treating OIs	Nystatin, fluconazole, ketoconazole and itraconazole are effective treatments for oral candidiasis.	Patton et al	1-A	
Treating OIs	Pegylated liposomal doxorubicin appears to give a superior response rate and cause a similar number of adverse events compared to standard regimens when used among patients with advanced KS.	Dedicoat (Cochrane)	1-A	
Treating OIs	Alitretinoin gel appears effective and safe for use in the treatment of cutaneous KS, among patients with a relatively high performance status.	Dedicoat (Cochrane)	1-A	

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EFFECTIVE INTERVENTIONS, continued				
Treating OIs	Radiotherapy is effective in treating cutaneous lesions with higher doses being associated with a more prolonged response at the expense of greater toxicity.	Dedicoat (Cochrane)	1-A	
Treating OIs	The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for HIV-infected patients with P carinii pneumonia who are unresponsive to conventional antipneumocystis agents.	Smego et al	2-B* <i>*Based on article's abstract summary – unable to review complete article.</i>	
Treating OIs	The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for HIV-infected patients with P carinii pneumonia who are unresponsive to conventional antipneumocystis agents.	Dedicoat (Cochrane)	1-A	
Palliative care	Evidence shows that performing constant or interval aerobic exercise, or a combination of constant aerobic exercise and progressive resistive exercise for at least 20 minutes three times a week for at least four weeks appears to be safe and may be able to improve cardiopulmonary fitness and psychological well-being for adults living with HIV/AIDS.	Nixon et al (Cochrane)	1-A	
Palliative care	Testosterone therapy may be considered in patients with HIV wasting syndrome to reverse muscle loss, but there is a concern about the adverse metabolic effects of long-term testosterone administration and long-term follow-up for these patients is needed.	Kong & Edmonds	1-B	
Palliative care	Stress management in HIV-infected individuals was found to be beneficial for decreasing anxiety and improving self-esteem and CD4 counts.	Ozsoy	1-A	

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EFFECTIVE INTERVENTIONS, continued				
Palliative care	The use of standard antidepressants (imipramine, fluoxetine, and sertraline) or alternative antidepressants (dextroamphetamine and testosterone replacement therapy) are all effective in the treatment of clinical depression among patients with HIV; since each possesses relatively unique benefits, many valuable treatment options are available to address the individual needs of patients.	Wagner et al	1-B	
MORE RESEARCH NEEDED				
Palliative care	Many HIV-infected individuals use complementary medicines for caring for HIV infection (acupuncture, herbal medications, stress reduction and vitamins being the most widely used) but the benefits and risks need further investigation.	Ozsoy		
Palliative care	More high quality research is needed to determine the effectiveness of herbal medications to relieve symptoms such as diarrhea and nausea in HIV-infected individuals.	Liu et al (Cochrane – in peer review)		
Palliative care	Larger, more rigorous studies are needed to determine the effectiveness of different forms of palliative care (such as hospital based vs. home based care, the use of coordinating nurses vs. conventional care).	Salisbury et al		
Palliative care	Aerobic exercise interventions were found to be effective, but further studies are needed to investigate the effects in people living with HIV/AIDS who are children, teens, or older adults since the studies exclusively considered adults between the ages of 18- 50 years old. The effects of exercise among females demands further attention as females were under-represented in the identified trials.	Nixon et al (Cochrane)		

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MORE RESEARCH NEEDED, continued				
Treating OIs	Although standard rifampin containing short-course regimens are very effective in treating pulmonary tuberculosis in healthy immunocompetent people, the optimal duration of therapy for tuberculosis in HIV-infected patients is controversial. Some experts have suggested that all HIV-related tuberculosis should be treated with a longer course of therapy, regardless of evidence of early response to therapy. Further assessment of the optimal therapy duration is needed.	Pai M. (Cochrane protocol)		
Preventing OIs	Although cotrimoxazole has been shown to be effective in western Africa, further trials are needed to determine wider applicability of these findings, particularly in areas with higher background bacterial resistance to cotrimoxazole.	Grimwade et al (1) (Cochrane)		
Preventing OIs	The effectiveness of routinely administered cotrimoxazole on death and illness episodes in children with HIV infection, and in infants of HIV infected mothers' needs to be assessed.	Grimwade et al (2) (Cochrane)		
Treating OIs	More research is needed to determine the efficacy of valganciclovir, a new oral agent for the therapy of cytomegalovirus (CMV) retinitis is shown to be effective in the treatment of CMV retinitis in HIV-positive patients, and has easy administration and a lack of potential catheter-related complications.	Cocohoba & McNicholl		
Palliative care	Rigorous studies are needed to identify if telling the truth about patients' condition has a positive or negative effect on their psychological distress when receiving palliative care.	Leliopoulo et al		
Preventing OIs	Further research is needed to determine if dapsone is effective for use as a secondary PCP prophylaxis.	Saillour-Glennison et al		
ARV for HIV infection	Controlled trials are urgently needed to determine which interventions can significantly improve adherence to HAART. Whether interventions that improve adherence also suppress viral load and improve clinical outcomes should also be considered.	Haddad et al (Cochrane)		

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MORE RESEARCH NEEDED, continued				
ARV for HIV infection	Interventions to promote adherence that focus on the provider and the patient-provider relationship, variables related to the treatment regimen or illness and contextual factors are all needed. Also investigations into the timing of when to begin the intervention in patients are needed.	Simoni et al		
ARV for HIV infection	There is a need for interventions to address provider and patient-provider relationships to promote adherence to ARVs as well as interventions targeting special groups of patients such as children and drug users	Simoni et al		
ARV for HIV infection	Research is needed to determine the efficacy of planned structured treatment interruptions as a way to decrease the drug-taking burden, side effects and costs associated with ARV therapy.	Pai N. et al (Cochrane – in peer review)		
Treating OIs	The majority of treatment options for patients with Kaposi's sarcoma in resource poor settings are unlikely to be available or affordable in developing countries where the bulk of HIV infection and KS occur, apart from radiotherapy that may be available in a few tertiary centres. Recent changes in pricing mean that HAART is likely to become more available to developing countries in the near future. In this context, trials designed to look at the effect of cheaper and more widely available chemotherapeutic agents for the treatment of HIV associated KS among patients already on HAART are a priority. One such trial is underway in South Africa.	Dedicoat (Cochrane)		
ARV for HIV infection	Further studies are needed for diagnostic and prognostic tests to be used in resource limited settings such as the develop a rapid, portable CD4 test and surrogate tests for viral load and CD4 count.	Torre et al		

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MORE RESEARCH NEEDED, continued				
Treating OIs	More research is needed to determine the most effective regimen of isoniazid for preventing active TB in HIV-infected patients with latent TB. The choice of regimen will depend on factors such as cost, adverse effects, adherence and drug resistance. In addition, trials evaluating the long-term effects of anti-tuberculosis chemoprophylaxis and the influence of level of immunocompromise on effectiveness are needed.	Woldehanna et al (Cochrane)		
Treating OIs	Further research is needed to determine the optimal duration of therapy for active tuberculosis in HIV-infected patients.	Pai M. et al (Cochrane protocol)		
Treating OIs	More research is needed to determine the efficacy and cost-effectiveness of antifungals for the primary prophylaxis of cryptococcal disease in resource limited settings.	Chang et al (Cochrane, in progress)		
ARV for HIV infection	Research is needed to assess strategies to scale up the implementation of ARV treatment in resource-limited settings in order to guarantee an infrastructure exists to provide ARVs as well as support and counseling to HIV-infected patients.	Hammer et al		
ARV for HIV infection	Additional strategies to scale up ARV therapy management that need further investigation include: low-cost approaches to CD-4 cell count and viral load monitoring, monitoring for treatment failure and drug toxicities as well as strategies to improve the affordability and sustainability of drug financing.	Hammer et al		