



HIV/AIDS

PREVENTION, TESTING AND TREATMENT:
Evidence from Cochrane systematic reviews

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INTRODUCTION

Human immunodeficiency virus (HIV) is a major public health issue. In Sub-Saharan Africa, 24 million people are living with the disease and almost 70% of the world's new HIV infections come from this region.

What is a Cochrane systematic review?

A Cochrane systematic review asks a specific research question about a specific healthcare intervention in a clearly defined group of people who have a health condition or problem, for example does the use of antiretroviral drugs reduce the risk of mother-to-child transmission of HIV infection? Researchers use the best research evidence published around the world to answer to the question. These summaries are called Cochrane Reviews. They include a plain language summary for the public. The reviews are produced by The Cochrane Collaboration and published in an online database, *The Cochrane Library* (www.thecochranelibrary.com). In 2013 the World Health Organization (WHO) developed guidelines for the prevention and treatment of HIV infection (<http://www.who.int/hiv/pub/guidelines/arv2013/en/>). This booklet contains plain language summaries of HIV/AIDS Cochrane Reviews published between 2010 and 2014. Some of these informed the WHO guidelines.

The South African Cochrane Centre (SACC)

The SACC (www.mrc.ac.za/cochrane) is based at the South African Medical Research Council in Cape Town. It is part of the international Cochrane Collaboration (www.cochrane.org), a non-profit organization. The vision of the SACC is that healthcare decision-making within Africa is informed by high quality, timely and relevant research evidence.

The Cochrane Consumer Network (CCNet)

The CCNet consists of people committed to the importance of consumer participation in informed healthcare decision-making. CCNet offers communication support and training to enable people to use the Cochrane Reviews to make well-informed healthcare decisions. To learn more about CCNet visit their website: <http://consumers.cochrane.org/healthcare-users-cochrane>

Antiretroviral drugs

Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Antiretroviral drugs have been shown to reduce risk of mother-to-child transmission of HIV and are also widely used for post-exposure prophylaxis for parenteral and sexual exposures. Sexual transmission may be lower in couples in which one partner is infected with HIV and the other is not and the infected partner is on antiretroviral therapy (ART).

Summary:

Antiretroviral drugs can prevent transmission of HIV from an infected sexual partner to an uninfected one, by suppressing viral replication. We found one randomised controlled trial and nine observational studies that examined this question. Overall we found that in couples in which the infected partner was being treated with antiretroviral drugs the uninfected partners had, at worst, more than 40% lower risk of being infected than in couples where the infected partner was not receiving treatment. Since the World Health Organization (WHO) already recommends antiretroviral treatment for all persons with ≤ 350 CD4 cells/ μL , we also examined studies that had studied couples in which the infected partners had CD4 counts higher than this level. We found that there is strong evidence from the randomised controlled trial that in this group HIV was less likely to be transmitted to uninfected partners from treated infected partners than from untreated infected partners.

Citation:

Anglemyer A, Rutherford GW, Horvath T, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.: CD009153. DOI: 10.1002/14651858.CD009153.pub3

Behavioral and social

Behavioral interventions to promote condom use among women living with HIV

High rates of HIV infection among women of reproductive age have dramatic consequences for personal and public health. Prophylaxis during sexual intercourse in the form of condoms has been the most effective way to prevent both STI and HIV transmission among people living with HIV

Summary:

Behavioral interventions to promote condom use and/or to modify HIV sexual risk behaviours include individual counseling, skills training, coping strategies, peer education, and social and educational support. This systematic review of randomized controlled trials assessed the effects of behavioral interventions on promoting condom use among women living with HIV, a population at higher risk to other sexually transmitted infections (STIs). Based on five eligible studies, we found that behavioral interventions promoting consistent condom use in HIV-positive women did not have a significant impact on outcomes, when compared to standard care or minimal HIV-related support. However, these findings should be used with caution since they are based on a few small trials that were targeted specifically towards HIV-positive women. New research is needed to assess the potential personal and public health gains that could arise from a combination of interventions that promote safe sexual behavior and adopt a harm reduction approach, particularly in developing countries, where HIV infection rates among women remain high.

Citation:

Carvalho FT, Gonçalves TR, Faria ER, Shoveller JA, Piccinini CA, Ramos MC, Medeiros LRF. Behavioral interventions to promote condom use among women living with HIV. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD007844. DOI: 10.1002/14651858.CD007844.pub2

Behavioral interventions to reduce HIV incidence and HIV/STI prevalence among female sex workers in low- and middle-income countries

The rates of HIV and sexually transmitted infection (STI) transmission continue to increase, particularly among sex workers and their clients in low- and middle-income countries. Prevention efforts directed towards these infections in this at-risk population may have had an effect in reducing the overall transmission of HIV/STIs in the general population.

Summary:

Several successful behavioral interventions have been reported including interventions to reduce HIV/STI incidence and prevalence, change behavior, promote condom use, improve condom availability, and increase sexual health knowledge. The review found seven individual randomised controlled trials (RCTs), two cluster-RCTs and four quasi-RCTs involving 8,698 participants examining a variety of behavioral interventions to evaluate whether they reduced HIV/STIs rates or resulted in changed behavior among sex workers and their clients. Results showed that the interventions were effective in HIV/STI prevention, including reducing the incidence and prevalence of HIV and STIs. Furthermore, there were some differences in self-reported behavior including increased condom use and a reduction in the risk of drug use. However, these trials were small and generally had few participants. As a result, evidence for the effectiveness of social cognitive theory and promoting condom use in reducing HIV/STI incidence compared to other behavioral interventions was limited, because no RCTs examined the effects of these interventions on HIV prevalence or on sex workers other than female sex workers. In future research and program agendas should assess other potentially more potent behavioral change strategies.

Citation:

Wariki WMV, Ota E, Mori R, Koyanagi A, Hori N, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low- and middle-income countries. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD005272. DOI: 10.1002/14651858.CD005272.pub3

Behavioral interventions to reduce HIV transmission among sex workers and their clients in high-income countries

Interventions to change behaviour among sex workers and their clients have been identified as a strategy to reduce HIV transmission.

Summary:

Behavioural interventions, such as individual counselling, voluntary counselling and testing, peer education, negotiation skills for using a condom with their clients, assertiveness and relationship support, discussing attitudes and beliefs, videos and role-playing, may reduce the prevalence of sexually transmitted infections (STI) and improve the knowledge of HIV transmission among sex workers and their clients. The review found four studies, comprising two RCTs and two quasi-experimental pretest-posttest trials with control groups involving 1,795 participants. No trials reported HIV prevalence/incidence as outcomes. Further RCTs that test for the identification of effective interventions for HIV prevention with outcomes of biological endpoints, such as HIV incidence or prevalence, are needed for these neglected populations. More research is also needed for male or transgender sex workers and their clients in high-income countries.

Citation:

Ota E, Wariki WMV, Mori R, Hori N, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD006045. DOI: 10.1002/14651858.CD006045.pub3

Interventions to modify sexual risk behaviours for preventing HIV in homeless youth

Homeless youth are at high risk for HIV infection as a consequence of risky sexual behaviour. Interventions for homeless youth are challenging. Assessment of the effectiveness of interventions to modify sexual risk behaviours for preventing HIV in homeless youth is needed.

Summary:

There have been a limited number of rigorously conducted interventions to modify the sexual behaviour of homeless youth 12-24 years of age to prevent them from acquiring HIV. More research is required to identify effective strategies for this population. In this review, we systematically searched published and unpublished accounts of interventions that had been rigorously tested. We found three eligible independently conducted randomised controlled trials testing three different interventions. All three were conducted in the United States, amongst a total of 615 homeless, male and female youth. Due to the varied delivery of interventions, outcome measurement and reporting, we were unable to aggregate outcomes to estimate summary of effect measures. The significant risk of bias associated with the three included studies and their heterogeneity necessitate caution in interpreting the effectiveness of interventions to modify sexual risk behaviour for preventing HIV in homeless youth. While studies among homeless youth are highly challenging, future trials should comply with rigorous methodology in design, delivery, outcome measurement and reporting as well as consider the changing facets of homeless youth when designing HIV prevention tools.

Citation:

Naranbhai V, Abdool Karim Q, Meyer-Weitz A. Interventions to modify sexual risk behaviours for preventing HIV in homeless youth. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007501. DOI: 10.1002/14651858.CD007501.pub2

Interventions to reduce risky sexual behaviour for preventing HIV infection in workers in occupational settings

Even though there is considerable achievement in the fight against HIV/AIDS, in terms of reduction in number of new infections and deaths from AIDS-related illnesses, the impact of HIV in the community and the work environment is great. The workplace provides an important avenue to prevent HIV.

Summary:

Eight studies with 11,164 participants were included but one study did not provide enough data to be useful. One study from Africa found a strong increase in uptake of Voluntary Counseling and Testing (VCT) to 51% when delivered on-site which was 14 times more compared to a voucher for off-site testing. However, VCT did not change HIV incidence in one study among African factory workers. In another study among Hong Kong truck drivers, VCT decreased self-reported sexually transmitted diseases (STDs) but VCT did not decrease unprotected sex significantly. Education was studied among soldiers in Nigeria, Angola and the US, truck drivers in India and factory workers in Thailand. Education that was modelled after a motivational theory reduced STDs with 32%, decreased unprotected sex with a small amount, reduced sex with a commercial sex worker with 12% but did not decrease the number of partners or the habit of using alcohol before sex.

Citation:

Ojo O, Verbeek JH, Rasanen K, Heikkinen J, Isotalo LK, Mngoma N, Ruotsalainen E. Interventions to reduce risky sexual behaviour for preventing HIV infection in workers in occupational settings. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD005274. DOI: 10.1002/14651858.CD005274.pub3.

Population-based biomedical sexually transmitted infection control interventions for reducing HIV infection

The transmission of sexually transmitted infections (STIs) is closely related to the sexual transmission of human immunodeficiency virus (HIV). Similar risk behaviours, such as frequent unprotected intercourse with different partners, place people at high risk of HIV and STIs, and there is clear evidence that many STIs increase the likelihood of HIV transmission. STI control, especially at the population or community level, may have the potential to contribute substantially to HIV prevention.

Summary:

Community- or population-based sexually transmitted infection control does not appear to be an effective HIV prevention strategy in most settings. In the early 1990s, improved STI treatment services were shown to reduce HIV incidence in northern Tanzania, in an environment characterised by an emerging HIV epidemic, where STI treatment services were poor and where STIs were highly prevalent. Subsequent trials, however, failed to confirm these findings and also failed to show a substantial benefit for community-wide presumptive treatment for STIs. This is likely due to the endemic nature of HIV and relatively low incidence of STIs in these populations. There are, however, other good reasons as to why STI treatment services should be strengthened and the available evidence suggests that when an intervention is applied and accepted in a community, it can improve the quality of services provided. The trial in Masaka District, Uganda showed an increase in the use of condoms, a marker for less risky sexual behaviours, although a newer study conducted in Zimbabwe suggested no effect. With the last three trials having shown disappointing results with respect to HIV prevention, it is unlikely that further community trials will be conducted, let alone yield different results. Future trials of biomedical interventions that involve individual randomisation, however, may represent an opportunity to reexamine presumptive treatment of STIs. Such trials should also aim to measure a range of factors that include health-seeking behaviour and quality of treatment, as well as HIV, STI and other biological endpoints.

Citation:

Ng BE, Butler LM, Horvath T, Rutherford GW. Population-based biomedical sexually transmitted infection control interventions for reducing HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD001220. DOI: 10.1002/14651858.CD001220.pub3

Psychosocial interventions for reducing injection and sexual risk behaviour for preventing HIV in drug users

Drug users (including both injection drug users and crack cocaine users), are at high levels of risk for contracting HIV. Therefore it is important to reduce the injection and/or sexual risk behaviours of these groups both for the benefit of themselves and for society as a whole.

Summary:

People who misuse drugs are at greater risk of developing HIV. Interventions designed to reduce this risk have been developed. There were 35 trials on 11,867 participants that examined whether these interventions are effective in reducing sexual and injection behaviour associated with greater risk of developing HIV. There are not large differences in effectiveness between multi-session psychosocial interventions and briefer interventions. This suggests brief educational interventions are more likely to be cost-effective and may be more readily implemented in a variety of different context.

Citation:

Meader N, Li R, Des Jarlais DC, Pilling S. Psychosocial interventions for reducing injection and sexual risk behaviour for preventing HIV in drug users. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD007192. DOI: 10.1002/14651858.CD007192.pub2

Telephone delivered interventions for preventing HIV infection in HIV-negative persons

Although HIV infection can be prevented, still a large number of new infections occur. More effective HIV prevention interventions are needed to reduce the number of people newly infected with HIV. Phone calls can be used to potentially more effectively deliver HIV prevention interventions. They have the potential to save time, reduce costs and facilitate easier access.

Summary:

Interventions that teach people about HIV can change their attitudes and behaviour, and thereby prevent new HIV infections. These interventions often require people to go to health facilities, but barriers such as a lack of money, transport problems or stigma attached to HIV-positive serostatus can limit people's access to HIV prevention interventions. Landline or mobile phones calls can be used to potentially more effectively deliver HIV prevention interventions, because they may save people's time, reduce costs and give people easier access to healthcare.

The aim of this review was to assess the effectiveness HIV prevention interventions delivered by phone calls compared to the standard way of delivering care. After a comprehensive search of various scientific databases and other resources, we found only one relevant study. This study was done in sexual assault services in South Africa. Study participants were women and girls who were given medication to prevent HIV infection (so called 'post-exposure prophylaxis' or 'PEP') after they had been raped. The participants were divided into two groups: one group of participants only received standard care and participants in the other group were given standard care and support via telephone calls to help them take their HIV prevention medication. Overall, only about one third of the participants took their HIV prevention medication for 28 days. The participants who received the phone calls were not more likely to take their medication than participants who only received standard care. Also, the phone calls did not decrease the number of participants with depression and did not increase the number of participants who read an information pamphlet or returned to collect HIV prevention medication. Only a higher percentage of participants who received the calls used a medication diary compared to the participants who did not receive the calls. No harmful effects of this intervention were reported. We could not find any information about other relevant outcomes, such as participants' and healthcare

providers' satisfaction with the telephone intervention or costs. We urgently need more studies conducted in various settings comparing the effectiveness of the phone calls to other ways of delivering HIV prevention interventions to prevent new HIV infections.

Citation:

van-Velthoven MHMMT, Tudor Car L, Gentry S, Car J. Telephone delivered interventions for preventing HIV infection in HIV-negative persons. *Cochrane Database of Systematic Reviews* **2013**, Issue 5. Art. No.: CD009190. DOI: 10.1002/14651858.CD009190.pub2

Mother-to-child transmission

Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Antiretroviral drugs reduce viral replication and can reduce mother-to-child transmission of HIV either by lowering plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. In rich countries, highly active antiretroviral therapy (HAART) which usually comprises three drugs, has reduced the mother-to-child transmission rates to around 1-2%, but HAART is not always available in low- and middle-income countries. In these countries, various simpler and less costly antiretroviral regimens have been offered to pregnant women or to their newborn babies, or to both.

Summary:

At the end of 2009, 2.5 million children under the age of 15 years were estimated to be living with HIV/AIDS. The majority of these children acquired their infections as a result of mother-to-child transmission during pregnancy, labor, or breastfeeding. Antiretroviral drugs administered to the HIV-infected mother and/or to her child during pregnancy, labor, or breastfeeding can reduce mother-to-child transmission of HIV. The objective of this review is to determine whether a regimen of antiretroviral drugs leads to a significant reduction in HIV transmission during pregnancy and labor without serious side-effects.

The 25 trials found eligible for this review included 18,901 participants. The included trials compared the use of antiretrovirals versus placebo, longer regimens versus shorter regimens using the same antiretrovirals, and antiretroviral regimens using different drugs and drug combinations. This review of trials found that short courses of certain antiretroviral drugs are effective in reducing mother-to-child transmission of HIV, but are not associated with any safety concerns in the short term.

Citation:

Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD003510. DOI: 10.1002/14651858.CD003510.pub3

Male involvement for increasing the effectiveness of prevention of mother-to-child HIV transmission (PMTCT) programmes

Despite efforts to increase the uptake of prevention of mother to child transmission of HIV (PMTCT) services, coverage is still lower than desired in developing countries. A lack of male partner involvement in PMTCT services is a major barrier for women to access these services.

Summary:

Over the years, national governments and international agencies have strengthened the implementation of PMTCT programmes. However, the majority of women still do not access these services. In 2010 there were 390,000 new HIV infections in children, 90% of which were infected through vertical transmission. Research has shown that fear of violence or abandonment by male partners, cultural gender rules and disparate decision making power for women are among the main reasons that women do not access PMTCT services. Thus interventions should focus on promoting gender equality and improving male awareness and engagement in their families' health in order to improve uptake of PMTCT services. We aimed to assess the effectiveness of male involvement interventions on women's uptake of PMTCT services in developing countries.

We undertook a comprehensive search to identify relevant studies. We found 3,072 references, but only one study that met our criteria. The study was performed in 2003-2004 in Tanzania. Pregnant women in the intervention group were provided with a letter inviting their male partners to accompany them to their next visit, in which they were offered voluntary HIV counselling and testing (VCT) together or separately. Women in the control group received the VCT individually during their first visit. The proportions of women that received VCT and collected their HIV test results were significantly lower in the intervention group than in the control group. Most of the women in the intervention group did not return to the clinic for the subsequent visit and most of those that returned accompanied refused to receive VCT together with their male partners. The invitation letter had a negative impact on the PMTCT uptake in that setting. We urgently need more studies assessing different interventions to improve male engagement in PMTCT to identify the most successful approach for women to safely access health care for their own health and to deliver HIV negative children.

Citation:

Brusamento S, Ghanotakis E, Tudor Car L, van-Velthoven MHMMT, Majeed A, Car J. Male involvement for increasing the effectiveness of prevention of mother-to-child HIV transmission (PMTCT) programmes. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No.: CD009468. DOI: 10.1002/14651858.CD009468.pub2

Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection

Observational studies of pregnant women in sub-Saharan Africa have shown that low serum vitamin A levels are associated with an increased risk of mother-to-child transmission (MTCT) of HIV. Vitamin A is cheap and easily provided through existing health services in low-income settings. It is thus important to determine the effect of routine supplementation of HIV positive pregnant or breastfeeding women with this vitamin on the risk of MTCT of HIV, which currently results in more than 1000 new HIV infections each day world-wide.

Summary:

Mother-to-child transmission (MTCT) of HIV is the primary way that children become infected with HIV. More than 1000 children worldwide are infected in this way every day. Researchers theorized that giving vitamin A supplements to HIV-infected pregnant or breastfeeding women might make it less likely that their children would be infected with HIV. The primary objective of this review of randomised studies is to estimate the effect of vitamin A supplementation during pregnancy and/or breastfeeding on the risk of mother-to-child transmission of HIV infection. The secondary objectives are to estimate the effect of vitamin A supplementation on infant and maternal mortality and morbidity, and to describe any side effects for the mother and the new baby.

The authors found that currently available evidence does not support the use of vitamin A supplementation of HIV-infected pregnant or breastfeeding women to reduce MTCT of HIV, although there is an indication that vitamin A supplementation during pregnancy improves birth weight.

Citation:

Wiysonge CS, Shey M, Kongnyuy EJ, Sterne JAC, Brocklehurst P. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD003648. DOI: 10.1002/14651858.CD003648.pub3

Other prevention options

Male circumcision for prevention of heterosexual acquisition of HIV in men

Male circumcision is defined as the surgical removal of all or part of the foreskin of the penis and may be practiced as part of a religious ritual, as a medical procedure, or as part of a traditional ritual performed as an initiation into manhood. Since the 1980s, over 30 observational studies have suggested a protective effect of male circumcision on HIV acquisition in heterosexual men. In 2002, three randomised controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men commenced in Africa. This review evaluates the results of these trials, which analysed the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.

Summary:

Results from three large randomised controlled trials conducted in Africa have shown strong evidence that male circumcision prevents men in the general population from acquiring HIV from heterosexual sex. At a local level, further research will be needed to assess whether implementing the intervention is feasible, appropriate, and cost-effective in different settings.

Citation:

Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD003362. DOI: 10.1002/14651858.CD003362.pub2

Male circumcision for prevention of homosexual acquisition of HIV in men

Summary:

At present there is no completed randomised controlled trial that has assessed the effects of male circumcision on acquisition of HIV and other sexually transmitted infections among men who have sex with men (MSM). Results from observational studies suggest that circumcision may be protective among MSM who practice primarily insertive anal sex, but the role of male circumcision overall in the prevention of HIV and other sexually transmitted infections among MSM remains to be determined.

Citation:

Wiysonge CS, Kongnyuy EJ, Shey M, Muula AS, Navti OB, Aki EA, Lo YR. Male circumcision for prevention of homosexual acquisition of HIV in men. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD007496. DOI: 10.1002/14651858.CD007496.pub2

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

More than 30 years into the global HIV/AIDS epidemic, infection rates remain alarmingly high, with over 2.7 million people becoming infected every year. There is a need for HIV prevention strategies that are more effective. Oral antiretroviral pre-exposure prophylaxis (PrEP) in high-risk individuals may be a reliable tool in preventing the transmission of HIV.

Summary:

This review evaluated the effects of giving people at high risk for HIV infection drugs to prevent infection (called antiretroviral pre-exposure prophylaxis, or PrEP). We found six randomised controlled trials that assessed the effects of oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) versus placebo; TDF versus placebo, and daily TDF-FTC versus intermittent TDF-FTC. One of the trials had three study arms (TDF, TDF-FTC and placebo arm). The trials were carried out amongst different risk groups, including HIV-uninfected men who have sex with men, people in serodiscordant sexual relationships where one partner is infected and the other is not, and other high risk men and women. The findings suggest that the use of TDF alone or TDF+FTC reduces the risk of becoming infected with HIV. However, further studies are needed to evaluate the method of administration (daily versus intermittent dosing), long-term safety and cost effectiveness of PrEP in different risk groups and settings.

Citation:

Okwundu CI, Uthman OA, Okoromah CAN. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD007189. DOI: 10.1002/14651858.CD007189.pub3

Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples

Sperm washing is a term used to describe the process in which individual spermatozoa are separated from the seminal fluid. Sperm washing is used to prevent HIV transmission but allow conception in sero-discordant couples, where the male is HIV positive, but the female is HIV negative. This procedure is based on the observation that HIV cannot attach itself to spermatozoa, but it can be found in the fluid and cells surrounding spermatozoa.

Summary:

Sperm washing is a technique that concentrates and separates the seminal fluid from the sperm in HIV-positive males. HIV is known to reside in the semen of HIV-positive men. When a woman wants to get pregnant, she is artificially inseminated with the sperm after it is washed and becomes virus-free. Sperm washing is done with the help of a centrifuge. The centrifuge is a device that spins at a high speed to separate the sperm from the seminal fluid in a given sample of semen. The sperm is then purified in a solution twice, in order to clean other unwanted substances in it, including the HIV. This technique was first introduced in 1992 in Milan, Italy by Augusto Enrico Semprini and colleagues, with the aim of helping HIV positive couples to conceive a healthy baby and to ensure that females do not acquire the disease from an HIV-positive male. Nowadays, many couples opt for sperm washing because it prevents the female partner from getting infected with HIV and enables the HIV positive male to propagate a healthy family. However, this process can be very lengthy and expensive. It is very helpful if both partners understand sperm washing to be a risk-reduction method and not a risk-free method as, technically, the virus could still be present in the washed sample. There have been no reports of seroconversion in the female partner when semen has been correctly processed. Hence, the risks of not performing sperm washing need to be strongly discussed with sero-discordant couples.

Citation:

Eke AC, Oragwu C. Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008498. DOI: 10.1002/14651858.CD008498.pub2

Home-based HIV voluntary counselling and testing (VCT) for improving uptake of HIV testing

The low uptake of HIV voluntary counselling and testing (VCT) has hindered global attempts to prevent new HIV infections and has limited scale-up of HIV care and treatment. Globally, only 10% of HIV-infected individuals are aware of their HIV status. One approach to increase uptake is home-based HIV VCT, which may be effective in increasing the number of patients on treatment and preventing new infections.

Summary:

The HIV/AIDS epidemic remains a significant global health problem, especially in developing countries. The rate of uptake of voluntary counselling and testing (VCT) is low, and only about one in 10 eligible people have access to VCT in developing countries. Challenges of HIV testing include the difficulty of getting to testing sites and the cost of being tested. Researchers assumed that providing HIV testing or results or both in homes compared to in a healthcare facility would lead to higher uptake of HIV testing. This review attempted to evaluate this assumption. We found only one published study from developing countries and none from developed countries. The only study included in the review showed an increase in VCT uptake after home-based VCT intervention. Because of the limited evidence to date, however, further research is needed to evaluate if home-based VCT is better than facility-based VCT or other testing methods.

Citation:

Bateganya M, Abdulwadud OA, Kiene SM. Home-based HIV voluntary counselling and testing (VCT) for improving uptake of HIV testing. *Cochrane Database of Systematic Reviews* 2010, Issue 7. Art. No.: CD006493. DOI: 10.1002/14651858.CD006493.pub4

Voluntary counseling and testing (VCT) for changing HIV-related risk behavior in developing countries

Voluntary counseling and testing (VCT) continues to play a critical role in HIV prevention, care and treatment. In recent years, different modalities of VCT have been implemented, including clinic-, mobile- and home-based testing and counseling. This review assesses the effects of all VCT types on HIV-related risk behaviors in low- and middle-income countries.

Summary:

Learning one's HIV status and receiving counseling is an important step to receiving HIV-related care and treatment, but also an important intervention for potentially changing risk behaviors related to HIV. A systematic review of the literature and a quantitative assessment found that VCT is an effective strategy for reducing some HIV-related risk behaviors, including decreasing the number of sexual partners of participants. Condom use was also significantly increased among participants who tested HIV-positive during VCT. Future research is needed to understand how VCT can be delivered more effectively to maximize its potential as an HIV prevention strategy.

Citation:

Fonner VA, Denison J, Kennedy CE, O'Reilly K, Sweat M. Voluntary counseling and testing (VCT) for changing HIV-related risk behavior in developing countries. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD001224. DOI: 10.1002/14651858.CD001224.pub4

Home-based care for reducing morbidity and mortality in people infected with HIV/AIDS

Home-based care (HBC), to promote quality-of-life and limit hospital care, is used in many countries, especially where public health services are overburdened.

Summary:

Home-based care (HBC), to promote quality-of-life and limit hospital care, is used in many countries, especially where public health services are overburdened. The objective of this review was to assess the effects of HBC on morbidity and mortality in those with HIV/AIDS. A comprehensive search for clinical trials of HBC including all forms of treatment, care and support offered in the home was done. Eleven completed and two ongoing studies were identified. Studies were generally small and very few studies were done in developing countries. There was a lack of studies truly looking at the effect of home based care itself or looking at significant end points (death and progression to AIDS). Intensive home-based nursing significantly improved self-reported knowledge of HIV and medications, and self-reported adherence to medication. Another study, comparing proportion of participants with greater than 90% adherence, found statistically significant differences over time but no significant change in CD4 counts and viral loads. A third study found significant differences in HIV stigma, worry and physical functioning but no differences in depressive symptoms, mood, general health, and overall functioning. Comprehensive case management by trans-professional teams compared to usual care by primary care nurses had no significant difference in quality-of-life after 6-months of follow-up and average length of time on service. Home total parenteral nutrition had no significant impact on overall survival and rate of re-hospitalisation. Two trials comparing computers with brochures/nothing/standard medical care found no significant effect on health status, and decision-making confidence and skill, but a reduction in social isolation after controlling for depression. Two trials evaluating home exercise programmes found opposing results. Home-based safe water systems reduced diarrhea frequency and severity among persons with HIV in Africa.

Citation:

Young T, Busgeeth K. Home-based care for reducing morbidity and mortality in people infected with HIV/AIDS. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD005417. DOI: 10.1002/14651858.CD005417.pub2

Telephone communication of HIV testing results for improving knowledge of HIV infection status

Both in developed and developing countries there is a large proportion of people who do not know they are infected with HIV. Knowledge of one's own HIV serostatus is necessary to access HIV support, care and treatment and to prevent acquisition or further transmission of HIV. Using telephones instead of face-to-face or other means of HIV test results delivery could lead to more people receiving their HIV test results.

Summary:

Patients often need to return to the testing site to receive HIV test results and post-test counselling one to two weeks later after being tested. Frequently, people do not return for their HIV test results, particularly in developing countries. In this setting, barriers such as lack of money, transportation or stigma attached to HIV positive serostatus prevent people from collecting their HIV test results. However, the HIV test results could also be delivered by a single phone call, either by a fixed line or a mobile phone. Given the recent rise in mobile phone use in both developed and developing countries, telephone HIV test result notification could be an effective and feasible method for increasing the number of people receiving HIV test results. The aim of this review was to assess effectiveness of the telephone for HIV test result delivery, compared with face-to-face or other methods of HIV test result notification. After a comprehensive search of various scientific databases and other resources, we found only one relevant study. This study was performed in 1998-1999 in the United States on high-risk and homeless youth. The participants were offered an HIV test and told that their HIV test results would be available in two weeks. They were then divided into two groups; one that had to return to the testing site to get their HIV test results, and another that had the option of receiving HIV test results either by telephone or face-to-face at the testing site. Overall, less than half of participants received their HIV test results. Most participants in the telephone notification group opted for telephone rather than in person delivery of HIV test results. The proportion of youth receiving their HIV test results in the telephone group was significantly higher compared to the face-to-face group. However, since none of the participants in the telephone group were HIV positive, the study could not provide information about the effectiveness of telephone HIV test result delivery in people with HIV. In addition, we could not find any information about other

relevant outcomes such as participants' and providers' satisfaction with the telephone HIV test results delivery, cost or potential harmful effects of this intervention. We urgently need more studies conducted in various settings comparing the effectiveness of telephone to other ways of HIV test result delivery and providing other relevant information in addition to the proportion of people receiving their HIV test results.

Citation:

Tudor Car L, Gentry S, van-Velthoven MHMMT, Car J. Telephone communication of HIV testing results for improving knowledge of HIV infection status. *Cochrane Database of Systematic Reviews* **2013**, Issue 1. Art. No.: CD009192. DOI: 10.1002/14651858.CD009192.pub2

Social marketing interventions to increase HIV/STI testing uptake among men who have sex with men (MSM) and male-to-female transgender women

Social marketing interventions have been shown to both promote and change many health-related behaviours and issues. As the HIV epidemic continues to disproportionately affect MSM and transgender women around the world, social marketing interventions have the potential to increase HIV/STI testing uptake among these populations.

Summary:

Men who have sex with men and transgender women are disproportionately affected by HIV/AIDS worldwide. Unrecognized infections could be one of the driving forces of ongoing HIV transmission among these populations. Thus, it is important to promote HIV testing. Three studies (one with a control group and two without) were included in the analysis. Limited evidence suggests that multi-media social marketing campaigns can significantly increase HIV testing uptake among men who have sex with men. Future research should employ more rigorous designs in evaluating social marketing interventions, measure their long-term impact, and identify intervention components that are most effective in reaching the target population and changing behaviours.

Citation:

Wei C, Herrick A, Raymond HF, Anglemyer A, Gerbase A, Noar SM. Social marketing interventions to increase HIV/STI testing uptake among men who have sex with men and male-to-female transgender women. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD009337. DOI: 10.1002/14651858.CD009337

TREATMENT

When to start

Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2 to 5 years old

The use of combination antiretroviral therapy (cART) comprising three antiretroviral medications from at least two classes of drugs is the current standard treatment for HIV infection in adults and children. Current World Health Organization (WHO) guidelines for antiretroviral therapy recommend early treatment regardless of immunologic thresholds or the clinical condition for all infants (less than one years of age) and children under the age of two years. For children aged two to five years current WHO guidelines recommend (based on low quality evidence) that clinical and immunological thresholds be used to identify those who need to start cART (advanced clinical stage or CD4 counts \leq 750 cells/mm³ or per cent CD4 \leq 25%).

Summary:

Antiretroviral combination therapy (cART) has been shown to be effective in slowing down the progression of AIDS and in reducing HIV-related illnesses and death. In infants and children who are diagnosed with HIV infection and are below two years of age the WHO recommends that cART should be started immediately. In children aged 2 to 5 years the WHO 2010 recommendations stated that treatment should be started when the body's defence system has started to weaken (as indicated by a decline in a child's CD4 cell count) or complications have occurred. This systematic review was undertaken to help inform the 2013 WHO guidelines which aimed to revise the recommendations of when to start therapy in 2 to 5 years old children. The authors identified two randomised controlled trials (RCTs) that compared immediate with deferred initiation of cART in HIV-positive children aged 1 to 12 years in Thailand or Cambodia. Additional analyses of 122 children enrolled in the two studies at ages 2 to 5 years were made available for this review. A cohort study from South Africa in HIV-positive children (median age 3.5 years) starting tuberculosis treatment and ART was also included. Results showed that we still lack enough evidence to determine whether early or late initiation of cART is best in children aged 2 to 5 years. The authors recognized the lack of evidence but highlighted the potential value of simplifying WHO recommendations to start cART in all children below five years with the goal of providing programmatic advantage to treatment programmes in resource-limited settings.

Citation:

Siegfried N, Davies MA, Penazzato M, Muhe LM, Egger M. Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2 to 5 years old. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD010309. DOI: 10.1002/14651858.CD010309.pub2

Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults

According to consensus, initiation of therapy is best based on CD4 cell count, a marker of immune status, rather than on viral load, a marker of virologic replication. For patients with advanced symptoms, treatment should be started regardless of CD4 count. However, the point during the course of HIV infection at which antiretroviral therapy (ART) is best initiated in asymptomatic patients remains unclear. Guidelines issued by various agencies provide different initiation recommendations according to resource availability. This can be confusing for clinicians and policy-makers when determining the best time to initiate therapy. Optimizing the initiation of ART is clearly complex and must, therefore, be balanced between individual and broader public health needs.

Summary:

Antiretroviral therapy (ART) has been shown to be effective in slowing down the progression of AIDS and in reducing HIV-related illnesses and death. Traditionally, therapy is administered based on a patient's CD4 cell count, where the number of CD4 cells reflects the body's immune (defence) system. An HIV-infected individual with a CD4 cell count of 500 cells/ μ L is considered healthy enough not to need ART. When a patient's cell count reaches 200 cells/ μ L, however, the immune system is severely weakened and ART is necessary. A patient with advanced symptoms receives treatment regardless of CD4 count.

Recommendations on the timing for ART initiation differ based on availability of resources, leading to confusion amongst clinicians and policy-makers in determining the most favourable point to begin treatment. The objective of this review is to assess the evidence for the optimal time to initiate ART in HIV-infected adults who have not previously received therapy and who do not have symptoms of HIV illness.

The authors reviewed two trials which involved 1,065 participants. Both studies compared the effect of ART initiation at high CD4 counts (350 cells/ μ L) with ART initiation at low CD4 counts (250 cells/ μ L). Results showed that starting ART at higher levels of CD4 reduces mortality rates in HIV-infected individuals who have not received antiretroviral treatment before and who do not have any symptoms of HIV illness.

Citation:

Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD008272. DOI:10.1002/14651858.CD008272.pub2.

Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age

In the absence of antiretroviral therapy (ART), over 50% of HIV-infected infants progress to AIDS and death by 2 years of age. However, there are challenges to initiation of ART in early life, including the possibility of drug resistance in the context of prevention of mother-to-child transmission (PMTCT) programs, a paucity of drug choices, uncertain dosing for some medications and long-term toxicities. Key management decisions include when to start ART, what regimen to start, and whether and when to substitute drugs or interrupt therapy. This review, an update of a previous review, aims to summarize the currently available evidence on this topic and inform the ART management in HIV-infected children less than 3 years of age.

Summary:

Children under 3 years of age who have HIV infection have a high risk of dying without antiretroviral therapy (ART). However, treatment in this age group is challenging because there are high levels of virus in the blood and few suitable drug choices. Results from this systematic review show that ART soon after birth is preferable to delaying treatment, because infants are less likely to die or become sick. Starting a first-line treatment regimen that includes lopinavir/ritonavir rather than nevirapine is preferable, because infants and young children are less likely to have to stop treatment, whether or not they had previously been exposed to nevirapine. However, lopinavir/ritonavir is more expensive than nevirapine. It is also currently only available as an inconvenient liquid, which tastes bitter and has to be refrigerated, making it challenging to implement in all parts of the world. While waiting for better formulations to become available, it may be possible to switch from lopinavir/ritonavir to nevirapine once the HIV virus levels become undetectable. However, based on the evidence currently available, a viral load test would be required to identify those children who could safely substitute lopinavir/ritonavir with nevirapine. Viral loads are expensive and not widely available in most countries in sub-Saharan Africa. An alternative treatment approach is to give a stronger drug combination (four different drugs together) when treatment is first started, then reduce down to three drugs after a short while. However, this strategy did not appear to have long-term benefits. A 'treatment interruption' strategy, in which infants start ART soon after birth but then stop medication after 1-2 years, is difficult to implement. Children stopping ART need to restart it very quickly to prevent them becoming sick, and monitoring a child off treatment is challenging in settings with few resources.

Citation:

Penazzato M, Prendergast AJ, Muhe LM, Tindyebwa D, Abrams E. Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD004772. DOI: 10.1002/14651858.CD004772.pub4

Optimal timing for antiretroviral therapy initiation in patients with HIV infection and concurrent cryptococcal meningitis

Currently, initiation of antiretroviral therapy (ART) in most patients with HIV infection is based on the CD4-positive-t-lymphocyte count. However, the point during the course of HIV infection at which ART should be initiated in patients with concurrent cryptococcal meningitis remains unclear. The aim of this systematic review was to summarise the evidence on the optimal timing of ART initiation in patients with cryptococcal meningitis for use in clinical practice and guideline development.

Summary:

Antiretroviral therapy has been shown to be effective in slowing down the progression of AIDS and in reducing HIV-related illnesses and death. Currently, this therapy is given based on a patient's CD4 cell count (the body's defense system). An HIV-infected individual whose meninges (the membranes covering the brain and spinal cord) are also infected by a fungus called *Cryptococcus neoformans* is considered very sick with his/her immune system severely weakened, and therefore will require ART.

At the moment, the best time to start ART in these patients is unclear. The objective of this review is to assess the evidence for the optimal time to initiate ART in people with HIV infection, who also have cryptococcal disease infection of the membranes covering their brain and spinal cord (meningitis).

The authors reviewed two trials which involved 89 participants. Both studies compared the effect of early ART initiation within the first month after starting treatment for fungi infection (*Cryptococcus neoformans*) to delayed ART initiation starting from the second month onwards. Results showed that we still lack enough evidence to determine whether early or late initiation of ART is best. However, the authors recommend that the initiation of ART in people with HIV infection who also have cryptococcal disease of the brain should be delayed until after some clinical improvement of the fungal disease is noted.

Citation:

Njei B, Kongnyuy EJ, Kumar S, Okwen MP, Sankar MJ, Mbuagbaw L. Optimal timing for antiretroviral therapy initiation in patients with HIV infection and concurrent cryptococcal meningitis. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD009012. DOI: 10.1002/14651858.CD009012.pub2

What to start with

Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naïve individuals

The introduction of highly active antiretroviral therapy (ART) as treatment for HIV infection has greatly improved mortality and morbidity for adults and children living with HIV around the world. Two of the most common medications given in first-line ART are the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT) and the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TDF).

Summary:

Deciding which treatment regimen to begin for first-line treatment in ART-naïve patients, however, remains a significant challenge. Two commonly used medications are tenofovir (TDF) and zidovudine (AZT). The purpose of this review was to assess which of these two medications was the best for initial treatment for people living with HIV, and through our search we identified two randomised controlled trials. We did not find any critical difference between the two medications in regards to serious adverse events or virologic response, but did find that TDF is superior to AZT in terms of immunologic response and adherence and more frequent emergence of resistance. However, these two studies are not directly comparable because they used two related different drugs in addition to TDF and AZT. Future studies and recommendations should focus on specific toxicities and tolerability when comparing these two medications.

Citation:

Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD008740. DOI: 10.1002/14651858.CD008740.

Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naïve individuals

The introduction of highly active antiretroviral therapy (ART) as treatment for HIV infection has greatly improved mortality and morbidity for adults and children living with HIV around the world. Two common medications given in first-line antiretroviral therapy are the nucleoside reverse transcriptase inhibitors (NRTI) stavudine (d4T) or zidovudine (AZT).

Summary:

Deciding which treatment regimen to begin for first-line treatment in ART-naïve patients, however, remains a significant challenge. Two of the most commonly used medications include stavudine (d4T) and zidovudine (AZT). The purpose of this review was to assess which of these two medications was the best for initial treatment for people living with HIV, and through our search we identified nine randomised controlled trials. Overall, these studies showed no critical difference between d4T and AZT. Future studies and recommendations should focus on specific toxicities and tolerability when comparing these two medications.

Citation:

Spaulding A, Rutherford GW, Siegfried N. Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD008651. DOI: 10.1002/14651858.CD008651.

Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals

The advent of highly active antiretroviral therapy (HAART) has reduced the morbidity and mortality due to HIV. The WHO antiretroviral treatment (ART) guidelines focus on three classes of antiretroviral drugs, namely: nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). Two of the most common medications given in first-line treatment are the NNRTIs, efavirenz (EFV) and nevirapine (NVP). It is unclear which NNRTI is more efficacious for initial therapy.

Summary:

The introduction of highly active antiretroviral therapy as treatment for HIV infection has greatly reduced mortality and morbidity for adults and adolescents living with HIV around the world. The recommended initial treatments for HIV infection include two drugs from a class of drugs known as nucleoside reverse transcriptase inhibitors (NRTI) and one from a related class of drugs called non-nucleoside reverse transcriptase inhibitors (NNRTI). The two NNRTIs currently in use are nevirapine (NVP) and efavirenz (EFV). NVP can cause liver damage and severe rash, both of which can be fatal. EFV may also cause a rash, impair mental function, and cause foetal malformations. The purpose of this review is to assess which of these two medications is better for initial treatment of HIV infection. We identified seven randomised controlled trials. A review of these trials shows that both drugs are equally effective in suppressing HIV infection but cause different side effects. Based on limited data, it appears that EFV is slightly less likely to cause side effects and more likely to prevent death than NVP. Future studies and recommendations should focus on specific toxicities and risk of resistance when comparing these two medications.

Citation:

Mbuagbaw LCE, Irlam JH, Spaulding A, Rutherford GW, Siegfried N. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database of Systematic Reviews* 2010, Issue 12. Art. No.: CD004246. DOI: 10.1002/14651858.CD004246.pub3

Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS

UNAIDS estimates that 34 million people are currently living with HIV worldwide. Currently recommended regimens for initiating HIV treatment consist of either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or ritonavir-boosted protease inhibitor (PI) combined with two nucleoside reverse transcriptase inhibitors (NRTIs). However, there may be some patients for whom NNRTIs and PIs may not be appropriate. This is an update of the review published in the Cochrane Library Issue 3, 2009.

Summary:

The primary objective of this review was to evaluate the antiviral efficacy of co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection. The secondary objectives were to evaluate the safety and tolerability of the triple drug combination. We identified 15 potentially eligible studies, four of which met our inclusion criteria. Our findings indicate that co-formulated abacavir-lamivudine-zidovudine remains a viable option for initiating antiretroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidaemia and those who do not tolerate ritonavir.

Citation:

Shey MS, Kongnyuy EJ, Alobwede SM, Wiysonge CS. Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS. *Cochrane Database of Systematic Reviews* **2013**, Issue 3, Art. No.: CD005481. DOI: 10.1002/14651858.CD005481.pub3.

When to switch

Optimal monitoring strategies for guiding when to switch first-line antiretroviral therapy regimens for treatment failure in adults and adolescents living with HIV in low-resource settings

One of the critical clinical decisions made in antiretroviral therapy (ART) is when to switch from an initial regimen to another due to treatment failure. This complex process requires consideration of multiple factors including: (1) what type of monitoring (e.g. clinical, immunologic, virologic) is available to guide switching; (2) establishing criteria for treatment failure (e.g. viral load >10,000 copies/mL); (3) integrating data from different types of monitoring; (4) making a decision; and, if possible, (5) follow-up and monitoring to determine patient outcomes. The initial step in this model of deciding when to switch is determining what type of monitoring for guiding when to switch is available and appropriate. This review seeks to find and summarize evidence on optimal monitoring strategies for guiding when to switch first-line regimens due to treatment failure among adults and adolescents living with HIV in low-resource settings.

Summary:

To provide the best possible care to patients with AIDS, it is important to decide correctly when to switch from one antiretroviral therapy to another for patients experiencing treatment failure. In low-resource settings, it appears that monitoring strategies which use immunologic or immunologic and virologic monitoring in addition to clinical monitoring for guiding when to switch therapy results in fewer patient deaths, fewer AIDS-defining illnesses, and fewer unnecessary switches. There is little evidence that adding virologic monitoring to immunologic monitoring has benefits. Further information on the studies, which are mostly currently reported in partial form, will give insight into this topic. Additionally, ongoing studies addressing when to switch likely will provide information to further clarify optimal monitoring strategies for guiding when to switch first-line therapy. Finally, cost-analysis studies will lend further insights into the relevance of these findings to low-resource settings.

Citation:

Chang LW, Harris J, Humphreys EH. Optimal monitoring strategies for guiding when to switch first-line antiretroviral therapy regimens for treatment failure in adults and adolescents living with HIV in low-resource settings. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No.: CD008494. DOI: 10.1002/14651858.CD008494

What to switch to

Antiretroviral regimens for patients with HIV who fail first-line antiretroviral therapy

Highly active antiretroviral therapy has reduced the morbidity and mortality of patients with HIV/AIDS. A common first-line ART regimen in low-resource settings includes a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs). If treatment failure occurs, a change to second-line therapy is necessary.

Summary:

Highly active antiretroviral therapy (HAART) has greatly reduced the illness and deaths of HIV-infected people worldwide. There are many options for first-line antiretroviral therapy (ART), but second-line therapy is necessary for people who fail the first-line treatment. This review attempted to assess the best ART regimen for HIV-infected people in low- and middle-income countries following treatment failure; however, the review found limited studies addressing this topic. One randomised trial and one abstract of an observational study evaluated whether or not to maintain lamivudine in second-line regimens; both suggested no difference in outcomes. There were no studies comparing boosted PI-containing second-line regimens in patients failing an NNRTI-based first-line regimen, nor any evaluating NRTI combinations after first-line with non-thymidine analog combinations. While such trials are difficult to conduct for a variety of reasons, randomised controlled trials comparing second-line therapies are needed, especially in resource-limited settings.

Citation:

Humphreys EH, Chang LW, Harris J. Antiretroviral regimens for patients with HIV who fail first-line antiretroviral therapy. *Cochrane Database of Systematic Reviews* 2010, Issue 6. Art. No.: CD006517. DOI: 10.1002/14651858.CD006517.pub3

Tuberculosis and HIV

Treatment of latent tuberculosis infection in HIV infected persons

Individuals with HIV infection are at an increased risk of developing active tuberculosis (TB). It is known that treatment of latent TB infection (LTBI), also referred to as TB preventive therapy or chemoprophylaxis, helps to prevent progression to active disease in HIV negative populations. However, the extent and magnitude of protection (if any) associated with preventive therapy in those infected with HIV should be quantified. This present study is an update of the original review.

Summary:

Most people infected with TB never get TB symptoms. This is called latent TB. People infected with HIV/AIDS are at increased risk of getting TB and about 30% of people with HIV who have latent TB will eventually get active TB. This results in an increase in the risk of earlier death. This update of the review of available clinical trials found that the risk of developing active TB was reduced when people infected with both HIV and TB used isoniazid. Isoniazid for latent TB is usually taken for six to 12 months, but more research is still needed to show optimal duration of treatment, the best treatment regime for people with HIV, and especially the best regimen in combination with HIV drugs.

Citation:

Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD000171. DOI: 10.1002/14651858.CD000171.pub3

Interventions for the prevention of mycobacterium avium complex in adults and children with HIV

Mycobacterium avium complex (MAC) infection is a common complication of advanced acquired immunodeficiency syndrome (AIDS) disease and is an independent predictor of mortality and shortened survival.

Summary:

Mycobacterium avium complex (MAC) infection is a common complication of advanced acquired immunodeficiency syndrome (AIDS) disease and can shorten the survival of these patients. We sought to examine effectiveness of all drugs for preventing MAC infection in adults and children with HIV infection. This review included eight trials conducted in the USA and Europe, published between 1993 and 2003.

We found evidence (very-low to low grade) that azithromycin or clarithromycin appeared to be a drug of choice for preventing MAC infection. There is a need for further studies to compare direct evidence between clarithromycin and azithromycin and studies to determine the optimal doses required for effective prevention of MAC infection.

Citation:

Uthman MMB, Uthman OA, Yahaya I. Interventions for the prevention of mycobacterium avium complex in adults and children with HIV. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.: CD007191. DOI: 10.1002/14651858.CD007191.pub2

Cancers

Interventions for squamous cell carcinoma of the conjunctiva in HIV-infected individuals

Squamous cell carcinoma of the conjunctiva is described in the ophthalmic literature as a rare, slow-growing tumour of the eye, normally affecting elderly men around 70 years of age. In Africa, however, the disease is different. The incidence is rising rapidly, affecting young persons (around 35 years of age), and usually affecting women. It is more aggressive, with a mean history of three months at presentation. This pattern is related to the co-existence of the HIV/AIDS pandemic, high HPV exposure, and solar radiation in the region. Various interventions exist, but despite therapy, there is a high recurrence rate (up to 43%) and poor cosmetic results in late disease. This review was conducted to evaluate the interventions for treatment of conjunctival squamous cell carcinoma in HIV-infected individuals.

Summary:

Conjunctival squamous cell carcinoma, a tumour of the thin membrane that covers the white of the eye, is becoming more common, more aggressive, and affecting more young people, especially women. This pattern is associated with the HIV/AIDS pandemic, exposure to solar radiation, and infection with human papilloma virus (HPV). Various treatment modalities exist, but the recurrence rate is high and the cosmetic outcome of late disease unsightly. Death may occur when the disease spreads to the surrounding structures and the brain. This review was conducted to evaluate the effects of the current interventions. No randomised controlled trials of any interventions for this cancer were found. Current clinical practice appears to be based on case series and case reports. These are weak sources of evidence for the effectiveness of a treatment. Randomised controlled clinical trials are needed.

Citation:

Gichuhi S, Irlam JH. Interventions for squamous cell carcinoma of the conjunctiva in HIV-infected individuals. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD005643. DOI: 10.1002/14651858.CD005643.pub3

Treatment of Kaposi sarcoma in children with HIV-1 infection

Kaposi sarcoma (KS) remains the second most frequently diagnosed HIV-related malignancy (HRM) worldwide and most common HRM in sub-Saharan Africa where HIV is most prevalent and human herpesvirus 8 (HHV-8), the precipitating agent for the development of KS, is endemic. The majority of KS patients would likely benefit from systemic chemotherapy in addition to the initiation of antiretroviral therapy (ART). However, as paediatric staging and treatment criteria are not readily available, there are no uniform treatment criteria.

Summary:

Using ART and chemotherapy together increases the likelihood of KS remission and reduces the risk of death in HIV-infected children diagnosed with KS. We found four observational studies that examined this question. Overall, we found that, though data are sparse and not adequately statistically adjusted, ART and chemotherapy together compared to chemotherapy alone and ART and chemotherapy compared to ART alone increases the likelihood of KS remission and reduces the risk of death in HIV-infected children diagnosed with KS. The quality of this evidence is, however, weak. Future clinical trials of KS treatment options in HIV-infected children are needed.

Citation:

Anglemyer A, Agrawal AK, Rutherford GW. Treatment of Kaposi sarcoma in children with HIV-1 infection. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD009826. DOI: 10.1002/14651858.CD009826.pub2

Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults

Kaposi's sarcoma remains the most common cancer in Sub-Saharan Africa and the second most common cancer in HIV-infected patients worldwide. Since the introduction of highly active antiretroviral therapy (HAART), there has been a decline in its incidence. However, Kaposi's sarcoma continues to be diagnosed in HIV-infected patients.

Summary:

Kaposi's sarcoma was the first tumor to be described in association with HIV infection and is an AIDS-defining condition. It is also known as Kaposi's sarcoma-associated herpes virus (KSHV) as Herpes virus 8 (HHV8) is recognized as an essential and necessary factor in the pathogenesis of KS. Nonetheless, not all HHV-8-infected individuals will develop the disease. The abnormal cells of KS form purple, red, or brown patches, plaques or tumors on the skin. There is no universally accepted system for staging Kaposi's sarcoma. The most commonly used staging system for AIDS-related KS in adults is the AIDS Clinical Trial Group (ACTG) staging.

This review evaluated the effects of highly active antiretroviral therapy (HAART) and chemotherapy, or different chemotherapy regimens for severe or progressive Kaposi's sarcoma in HIV infected adults.

We found six randomised controlled trials and three observational studies that assessed the effects of HAART plus chemotherapy compared with HAART alone; HAART plus chemotherapy compared with HAART plus another chemotherapy regimen; and chemotherapy compared with chemotherapy in the time before HAART was available. Of the nine included studies, seven included patients with a mix of mild to moderate (T0) Kaposi's sarcoma and severe (T1) Kaposi's sarcoma. There was no universal definition for what severity of disease was considered chemotherapy-requiring. For this review, we only extracted data for 792 HIV infected adults with severe Kaposi's sarcoma disease.

The findings from this review suggest that HAART plus chemotherapy may be beneficial in reducing disease progression compared to HAART alone in patients with severe or progressive Kaposi's sarcoma. For patients on HAART, in choosing among different chemotherapy regimens, there was no observed difference between liposomal doxorubicin, liposomal daunorubicin, and paclitaxel. The overall quality of evidence in this review can be described as moderate.

Citation:

Gbabe OF, Okwundu CI, Dediccoat M, Freeman EE. Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No.: CD003256. DOI: 10.1002/14651858.CD003256.pub2

Treatment for leiomyosarcoma and leiomyoma in children with HIV infection

Smooth muscle tumour (SMT) composed of leiomyoma and leiomyosarcoma recently has been described in many HIV-infected children. Leiomyosarcoma has become the second most frequent malignancy in children with HIV infection or other immunodeficiency diseases in the United States. Although leiomyosarcoma accounts for only 2% to 4% of childhood soft tissue sarcomas, the prognosis is poor in HIV-infected compared with non-infected patients. The development of Epstein-Barr virus (EBV)-associated SMT in children with acquired immunodeficiency virus (AIDS) decreases health, reduces quality of life, and often results in death. Some researchers, therefore, ascribe cause of death to SMT in the majority of these cases, not to AIDS. Currently, the optimal therapeutic strategy is controversial and there is a need to identify the efficacy and safety of different interventions for AIDS-associated SMT on overall survival and disease-free survival in children.

Summary:

There is a lack of reliable evidence on interventions for treating leiomyosarcoma and leiomyoma in children with HIV/AIDS. Smooth muscle tumour (SMT) is a type of cancer composed of leiomyoma and leiomyosarcoma. Although there are many more cases among adults with HIV infection than with children, an increasing number of SMTs have been described in HIV-infected children. There is a lack of uniform and effective therapies and their efficacy and safety still are unknown. No randomised controlled trials and clinical controlled trials of interventions for leiomyosarcoma and leiomyoma in children with AIDS were found that rigorously evaluated effectiveness.

Citation:

Yin X, Wu T, Yan Y, Zhang H, Bu H. Treatment for leiomyosarcoma and leiomyoma in children with HIV infection. *Cochrane Database of Systematic Reviews* 2010, Issue 5. Art. No.: CD007665. DOI: 10.1002/14651858.CD007665.pub2

Behavioural and social

Telephone delivered interventions for reducing morbidity and mortality in people with HIV infection

Telephone interventions, delivered either by landline or mobile phone, may be useful in the management of people living with HIV (PLHIV) in many situations. Telephone delivered interventions have the potential to reduce costs, save time and facilitate more support for PLHIV.

Summary:

More than 34 million people were living with HIV in 2010, and more than 2.7 million new infections occurred in that year. Improvements in drug treatments for HIV mean that the life expectancy of people living with HIV/AIDS (PLHIV) is now almost the same as that of non-infected people. However, the disease is still incurable, and patients require support to cope with their chronic illness and need for lifelong medication. Interventions often require people to go for face to face consultations, but barriers to healthcare, such as lack of money, transportation problems and the stigma sometimes associated with attending a clinic for HIV treatment, can prevent people from receiving the care they need. Using the telephone to deliver care to PLHIV may overcome some of these barriers, and ultimately improve health. It may also reduce costs, save time, and reduce effort. This could allow for a greater frequency of contact with patients, and the opportunity to reach more people in need of care. Mobile phones are widely used in both developed and developing countries, making them a feasible method to deliver health interventions for PLHIV.

The aim of this review was to assess the effectiveness of using the telephone to deliver interventions to improve the health of PLHIV compared to standard care. A comprehensive search of various scientific databases and other resources found 11 relevant studies. All of the studies were performed in the United States, and so the results may not apply to other countries, particularly developing countries. Some studies were aimed at any HIV positive person in the area in which the study was carried out, and others focused on specific groups of people, such as young substance using PLHIV, or older PLHIV. There were a lot of differences in the types of telephone interventions used in each study. There was some evidence that telephone interventions can improve medication adherence, reduce risky sexual behaviour, and reduce symptoms of depression in PLHIV. However, there were also

a number of studies that suggested that telephone interventions were no more effective than usual care alone. We need more studies conducted in different settings to assess the effectiveness of telephone interventions for improving the health of PLHIV.

Citation:

Gentry S, van-Velthoven MHMMT, Tudor Car L, Car J. Telephone delivered interventions for reducing morbidity and mortality in people with HIV infection. *Cochrane Database of Systematic Reviews* **2013**, Issue 5. Art. No.: CD009189. DOI: 10.1002/14651858.CD009189.pub2

Motivational interviewing for improving outcomes in youth living with HIV

Almost half of all the new HIV infections occur in youth. Motivational interviewing (MI) is a counselling technique that is effective in bringing about positive behavior changes in the general population. It is unclear whether it can be used to improve outcomes in youth living with HIV.

Summary:

Many young people are living with HIV. Motivational interviewing is a specific way of counselling which has been shown to be beneficial in the general population. It helps people adopt better health behaviours. It is not certain whether it can help youth living with HIV. We found two trials with a total of 237 participants which we included in this review. Both trials report that motivational interviewing can help young people to use condoms more often, and also to reduce the amount of HIV in their blood stream. One trial reports a reduction in alcohol use. Motivational interviewing did not affect retention in care. Some results of interest, like adherence to medication, number of deaths and quality of life were not reported by these trials, and should be reported in subsequent studies. Additionally, all these studies were conducted in a high income country therefore these results cannot be applied to low income countries.

Citation:

Mbuagbaw L, Ye C, Thabane L. Motivational interviewing for improving outcomes in youth living with HIV. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD009748. DOI: 10.1002/14651858.CD009748.pub2.

Other treatment options for HIV and related conditions

Prevention of diarrhoea in children with HIV infection or exposure to maternal HIV infection

Diarrhoea is a major cause of morbidity and mortality among infants and children worldwide, especially in low- and middle-income countries. HIV/AIDS is a condition that similarly disproportionately affects low- and middle-income countries; of the nearly 2.1 million children under age 15 years living with HIV/AIDS, the large majority reside in sub-Saharan Africa. Infants and children with HIV infection have more frequent and more severe diarrhoea than children without HIV. Interventions including vitamin A, zinc and cotrimoxazole may contribute substantially to preventing diarrhoea in children with HIV infection or exposure to HIV.

Summary:

Infants and children with HIV infection or maternal exposure through birth or breastfeeding to HIV infection may be more vulnerable to diarrhoea due to weakened immune systems, nutritional deficiencies or from having other infections. This review evaluated three interventions to assess whether they can prevent death or illness from diarrhoea in infants and children with HIV infection or exposure: vitamin A, zinc and cotrimoxazole. Vitamin A and zinc may correct micronutrient deficiencies that are prevalent in children with HIV infection or exposure, as well as prevent other infections. Cotrimoxazole is an antibiotic that helps prevent opportunistic infections in immunocompromised hosts, and may also prevent other infections. This review found nine studies that addressed these interventions in infants or children with HIV infection.

The review indicated that vitamin A shows reduction of mortality and morbidity due to diarrhoea in children with HIV infection and a trend in lower illness from diarrhoea. Zinc prevented visits due to watery diarrhoea and cotrimoxazole decreased death and respiratory infections.

Other outcomes were variable or did not reach significance. More research in this area would help clarify how these interventions impact illness from diarrhoea in children with HIV infection or exposure.

Citation:

Humphreys EH, Smith NM, Azman H, McLeod D, Rutherford GW. Prevention of diarrhoea in children with HIV infection or exposure to maternal HIV infection. *Cochrane Database of Systematic Reviews* **2010**, Issue 6. Art. No.: CD008563. DOI: 10.1002/14651858.CD008563.

Topical treatments for HIV-related oral ulcers

In HIV-infected adults, oral ulcers occur more frequently, last longer and produce more painful symptoms than in immunocompetent people. Oral aphthous ulcers observed during the course of HIV infection may be severe and can result in significant morbidity in these patients. Such manifestations may interfere with oral functions and alter patients' quality of life.

Summary:

Oral aphthous ulcers associated with HIV infection occur commonly and recur frequently with varying severity. They occur at different stages of the disease. Topical treatments aim at meeting the basic requirements of the management of these ulcers which include pain relief, healing and reduction in recurrence. Topical treatment reduces the incidence of toxicity and serious side effects associated with systemic treatments. This review was conducted to evaluate the efficacy of the various topical agents available for the treatment of HIV related oral aphthous ulcers. From all the abstracts and articles examined, only two studies appeared to meet the inclusion criteria but had no full text reports, which makes it impossible to make recommendations.

Citation:

Kuteyi T, Okwundu CI. Topical treatments for HIV-related oral ulcers. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD007975. DOI: 10.1002/14651858.CD007975.pub2

Treatment for anemia in people with AIDS

Anemia is common in persons with HIV infection and is associated with poor prognosis. There is a need to assess the effects of anemia treatments, and to determine whether these interventions are beneficial.

Summary:

There is a lack of reliable evidence on interventions for treating anemia in persons with HIV infection or AIDS. Persons with HIV infection or AIDS are more likely than the general population to develop anemia, and anemia is the most common blood disorder in the HIV/AIDS infected population. Compared to those who do not develop anemia, HIV-infected individuals who develop anemia are more likely to die early. It is important, therefore, to have good evidence regarding interventions that might be used to treat anemia. We found six randomised controlled trials (537 participants), all of which investigated recombinant human erythropoietin. It did not reduce mortality and transfusion requirements. Furthermore, recombinant human erythropoietin did not increase hemoglobin levels and improve quality of life in HIV-infected patients with anemia. All trials were judged to be of poor methodological quality.

Potential randomised trials should include outcomes such as mortality and quality of life, and pregnant women, children and all ethnic people.

Citation:

Martí-Carvajal AJ, Solà I, Peña-Martí GE, Comunián-Carrasco G. Treatment for anemia in people with AIDS. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD004776. DOI: 10.1002/14651858.CD004776.pub3.

Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children

Oral candidiasis (OC) associated with HIV infection occurs commonly and recurs frequently, often presenting as an initial manifestation of the disease. Left untreated, these lesions contribute considerably to the morbidity associated with HIV infection. Interventions aimed at preventing and treating HIV-associated oral candidal lesions form an integral component of maintaining the quality of life for affected individuals.

Summary:

This review evaluated the effects of interventions in preventing or treating oral thrush in children and adults with HIV infection. Thirty three trials (3445 participants) were included. Twenty two trials investigated treatment and eleven trials investigated prevention. There was no difference with regard to clinical cure between fluconazole compared to ketoconazole, itraconazole, clotrimazole and posaconazole. Fluconazole, gentian violet and ketoconazole were superior to nystatin. Compared to placebo and no treatment, fluconazole was effective in preventing clinical episodes from occurring. Continuous fluconazole was better than intermittent treatment. Insufficient evidence was found to come to any conclusion about the effectiveness of clotrimazole, nystatin, amphotericin B, itraconazole, ketoconazole or chlorhexidine with regard to OC prophylaxis.

Citation:

Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No.: CD003940. DOI: 10.1002/14651858.CD003940.pub3

Interventions for prevention and treatment of vulvovaginal candidiasis in women with HIV infection

Vulvovaginal candidiasis (vaginal thrush) is one of the most common fungal infections that recur frequently in HIV infected women. Symptoms of vaginal thrush are pruritis, discomfort, dyspareunia, and dysuria. Vulval infection presents as a morbilliform rash that may extend to the thighs. Vaginal infection is associated with white discharge, and plaques are seen on erythematous vaginal walls.

Summary:

Even though rarely or never resulting in systemic fungal infection or mortality, interventions for prevention and treatment of vaginal thrush is an essential part of maintaining the quality of life of such individuals. This review was aimed at evaluating such interventions.

The treatment aspect could not be evaluated as our search yielded no trials.

The search yielded two studies dealing with the preventive aspect of the condition. The first trial found weekly fluconazole significantly effective in preventing clinical episodes from occurring as compared to placebo. However, this regimen led to the emergence of species resistant to azoles.

The second trial with three arms of comparison; Clotrimazole, Lactobacillus and placebo gave no definitive results in preventing an episode of vaginal thrush.

Neither of the included studies investigated the effects of HAART or any other form of antiretroviral treatment on vaginal thrush nor did they explore difference in quality of life, viral shedding in vaginal secretions (infectivity), patient preference for route of administration or the cost.

Citation:

Ray A, Ray S, George AT, Swaminathan N. Interventions for prevention and treatment of vulvovaginal candidiasis in women with HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 8. Art. No.: CD008739. DOI: 10.1002/14651858.CD008739.pub2.

The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS

The use of cannabis (marijuana) or of its psychoactive ingredient delta-9-tetrahydrocannabinol (THC) as a medicine has been highly contested in many settings. There have been claims that smoked or ingested cannabis, either in its natural form or artificial form (pharmaceutically manufactured drug such as dronabinol), improves the appetites of people with AIDS, results in weight gain and lifts mood, thus improving the quality of life.

Summary:

The use of cannabis, its active ingredient or synthetic forms such as dronabinol has been advocated in patients with HIV/AIDS, in order to improve the appetite, promote weight gain and lift mood. Dronabinol has been registered for the treatment of AIDS-associated anorexia in some countries. However, the evidence for positive effects in patients with HIV/AIDS is limited, and some of that which exists may be subject to the effects of bias. Those studies that have been performed have included small numbers of participants and have focused on short-term effects. Longer-term data, and data showing a benefit in terms of survival, are lacking. There are insufficient data available at present to justify wide-ranging changes to the current regulatory status of cannabis or synthetic cannabinoids.

Citation:

Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* **2013**, Issue 4. Art. No.: CD005175. DOI: 10.1002/14651858.CD005175.pub3

Aerobic exercise interventions for adults living with HIV/AIDS

Access to combination antiretroviral therapy has turned HIV into a chronic and manageable disease for many. Exercise is a key strategy for people living with HIV and by rehabilitation professionals to address these disablements; however, knowledge about the effects of exercise among adults living with HIV still is emerging.

Summary:

Performing aerobic exercise or a combination of aerobic exercise and resistive exercise for at least 20 minutes, at least three times per week for at least five weeks appears to be safe and may improve fitness, body composition, and well-being for adults living with HIV.

Exercise is used by many people living with HIV to improve fitness, well-being, and body image. Exercise also is used as a strategy to diminish the health-related consequences of HIV and associated treatments. This review of 14 trials found 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 per week for at least five weeks appears to be safe and may be able to improve fitness, body composition, and well-being for adults living with HIV. More high-quality studies are needed to better evaluate the evidence on under-represented groups, such as women and older adults living with HIV, and those who discontinue their exercise programs.

Citation:

O'Brien K, Nixon S, Tynan AM, Glazier R. Aerobic exercise interventions for adults living with HIV/AIDS. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD001796. DOI: 10.1002/14651858.CD001796.pub3

Massage therapy for people with HIV/AIDS

Infection with HIV/AIDS is a pandemic that has affected millions of people globally. Although major research and clinical initiatives are addressing prevention and cure strategies, issues of quality of life for survivors have received less attention. Massage therapy is proposed to have a positive effect on quality of life and may also have a positive effect on immune function through stress mediation.

Summary:

People living with HIV/AIDS may experience a lower quality of life due to complications of the disease. Massage therapy may help people by improving their overall health and their ability to deal with stress. We systematically investigated studies that have compared massage therapy with other forms of therapy or no therapy. We found four randomised controlled trials that used massage therapy with children, adolescents or adults with HIV or late-stage AIDS. This review of the literature supports that massage therapy can benefit people with HIV/AIDS by improving quality of life, particularly if they receive the therapy in conjunction with other techniques, such as meditation and relaxation training, and provide more benefit than any one of these techniques individually. Furthermore, it may be that massage therapy can improve their body's ability to fight the disease; however, this is not yet convincingly proven. We recommend further studies be undertaken to investigate this question and recommend that in the meantime, people with HIV/AIDS use massage therapy to improve quality of life, provided they have clear goals and monitor their response to the therapy.

Citation:

Hillier SL, Louw Q, Morris L, Uwimana J, Statham S. Massage therapy for people with HIV/AIDS. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD007502. DOI: 10.1002/14651858.CD007502.pub2

Yellow fever vaccine for patients with HIV infection

Yellow fever (YF) is an acute viral haemorrhagic disease prevalent in tropical Africa and Latin America. The World Health Organization (WHO) estimates that there are 200,000 cases of YF and 30,000 deaths worldwide annually. Treatment for YF is supportive, but a live attenuated virus vaccine is effective for preventing infection. WHO recommends immunisation for all individuals > 9 months living in countries or areas at risk. However, the United States Advisory Committee on Immunization Practices (ACIP) advises that YF vaccine is contraindicated in individuals with HIV. Given the large populations of HIV-infected individuals living in tropical areas where YF is endemic, YF vaccine may be an important intervention for preventing YF in immunocompromised populations.

Summary:

In the United States of America, current guidelines do not recommend YF vaccine for individuals with HIV infection or AIDS; these recommendations, however, are targeted mostly at travellers to the parts of Latin America and Africa where YF occurs and who have the option of not going. For HIV-infected patients living in these areas where exposure is inevitable, it is important to weigh the risks of vaccination against the risk of developing YF. There are no known medicines for YF, further highlighting the importance of the vaccine. The purpose of this review was to assess the risks and benefits of YF vaccine for people living with HIV. We found three cohort studies that addressed this question. One study in children, from a time before effective widespread use of antiretroviral drugs, found that YF vaccine worked much less well in children with HIV than it did in those without HIV. Two studies in adults found that the immune response to YF vaccine was slightly lower in HIV-infected patients. No severe adverse events were observed in patients in these studies. However, because the numbers of people with HIV who have received YF vaccine is small, and serious side effects are uncommon in people without HIV infection, we are not certain about its safety. When it does need to be used, it should be given to people whose viral loads are low and CD4 counts are high.

Citation:

Barte H, Horvath TH, Rutherford GW. Yellow fever vaccine for patients with HIV infection. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD010929. DOI: 10.1002/14651858.CD010929.pub2.

Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection

Hepatitis B vaccine has been recommended for use in people living with HIV (PLHIV) mostly because of the similarities in routes of infection and their prevalence in the same geographic areas. PLHIV may not develop sero-protection after receiving standard hepatitis B vaccine due to their compromised immune status.

Summary:

This review seeks to determine whether vaccine for hepatitis B virus is effective in protecting people who have HIV against hepatitis B virus infection. It also seeks to determine if the vaccine is safe in people living with HIV.

Background

Hepatitis B virus infection can be acquired through contact with body fluids of infected people. Hepatitis B virus infection manifests with fever, yellowness of the eyes, abdominal pain and fatigue, but it can also be without symptoms especially in long standing infections. It can cause a persisting infection which can lead to liver complications and death. Hepatitis B virus infection and HIV infection are common in poorer countries and in these countries vaccines are not readily available. People living with HIV may not respond well to hepatitis B virus infection because of the weak ability for their bodies to develop resistance.

Study Characteristics

Our search for eligible papers was updated in August 2014 and we found one trial with 26 adult participants in Spain. The study sought to test if hepatitis B virus vaccine was better than placebo in preventing PLHIV from getting hepatitis B.

Key Results

The single study in this review showed improved immunity against hepatitis B among people living with HIV and taking antiretroviral therapy at 12 months. This immunity was lost once they stopped taking antiretroviral therapy. No side-effects were reported.

Quality of Evidence

The quality of evidence was assessed as very low.

Citation:

Okwen MP, Reid S, Njei B, Mbuagbaw L. Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No.: CD009886. DOI: 10.1002/14651858.CD009886.pub2.

ADHERENCE TO TREATMENT

Interventions to improve adherence to antiretroviral therapy in children with HIV infection

Achieving and maintaining high levels of medication adherence are required to achieve the full benefits of antiretroviral therapy (ART), yet suboptimal adherence among children is common in both developed and developing countries.

Summary:

Achieving and maintaining high levels of medication adherence are required to realise the full benefits of ART. We identified four studies that evaluated interventions designed to improve adherence to ART among children and adolescents age 18 years and younger. These studies showed that home-based nursing, peer support for adolescents and LPV/r-containing regimens have the potential to improve ART adherence, but more evidence is needed. Medication diaries do not appear to have an effect on adherence. There is a need for well-designed evaluations of interventions to improve paediatric adherence to ART.

Citation:

Bain-Brickley D, Butler LM, Kennedy GE, Rutherford GW. Interventions to improve adherence to antiretroviral therapy in children with HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD009513. DOI: 10.1002/14651858.CD009513

Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection

More than 34 million people are presently living with HIV infection. ART can help these people to live longer, healthier lives, but adherence to ART can be difficult. Mobile phone text-messaging has the potential to help promote adherence in these patients.

Summary:

Antiretroviral therapy can help people with HIV infection to live longer, healthier lives, but because of side-effects, adherence (taking these medications every day) can be difficult. Mobile phone text-messaging has the potential to help promote adherence in these patients.

Two randomised controlled trials from Kenya were included in the review. One trial compared short weekly text messages against standard care. The other trial compared short daily, long daily, short weekly and long weekly messages against standard care.

In the trial comparing only short weekly messages to standard care, text messaging was associated with lower risk of non-adherence at 12 months, and with the non-occurrence of virologic failure at 12 months.

Combining the data from both trials, weekly mobile phone text-messaging was associated with greater ART adherence at 48-52 weeks. The effect of short weekly text-messaging was also significant.

In the trial that compared different intervals and lengths for text-messaging to standard care, long weekly text-messaging was not significantly associated with a lower risk of non-adherence compared to standard care. Patients receiving weekly text-messages of any length were at lower risk of non-adherence at 48 weeks than were patients receiving daily messages of any length. There were no significant differences between weekly text-messaging of any length and between short or long messaging at either interval. Compared to standard care, any daily text-messaging, whether short or long, did not reduce the risk for non-adherence.

Weekly mobile phone text messages to patients on ART can help them to take their medication every day. It can also help to reduce the amount of HIV in their bloodstream. Because the two included trials were with adult patients only, there is a need for trials of this intervention with adolescents. Also, as the two trials were conducted in Kenya, a low-income country, there is a need for trials of this intervention in high-income countries.

Citation:

Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. *Cochrane Database of Systematic Reviews* **2012**, Issue 3. Art. No.: CD009756. DOI: 10.1002/14651858.CD009756

Micronutrient supplementation for children with HIV infection

Micronutrient deficiencies are widespread and compound the effects of HIV disease in children, especially in poor communities. Micronutrient supplements may be effective and safe in reducing the burden of HIV disease.

Summary:

This review includes 11 trials that tested the effectiveness and safety of various micronutrient supplements in children with HIV infection in a diversity of settings. All except one trial were conducted in African children. The primary outcomes were mortality, morbidity, and HIV-related hospitalisations, and secondary outcomes were HIV disease progression, measures of growth, and adverse effects of supplementation.

The review found that vitamin A supplements are beneficial and safe, and halved mortality overall in an analysis of three trials in different African countries. Zinc appeared to be safe and reduced diarrhoeal morbidity in one trial. Multiple micronutrient supplements reduced the duration of hospital admissions, and improved appetite and short-term growth in poorly nourished hospitalised children.

Further research is needed on single supplements other than vitamin A, and on the long-term effects, optimal composition and dosing of multiple supplements.

Citation:

Irlam JH, Siegfried N, Visser ME, Rollins NC. Micronutrient supplementation for children with HIV infection. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD010666. DOI: 10.1002/14651858.CD010666

Micronutrient supplementation in pregnant women with HIV infection

Micronutrient deficiencies are widespread and compound the effects of HIV disease; micronutrient supplements may be effective and safe in reducing this burden.

Summary:

Micronutrients are vital components of a person's daily food intake. Though only a small portion is necessary, a lack of micronutrients has been linked to tiredness, anaemia (low iron in blood), reduced learning ability, weaker immune system, and night blindness. In pregnant women, inadequate micronutrients have been shown to affect the development of the foetus and also the well-being of the mother. In regions with high HIV prevalence, food availability may be scarce, which could lead to a double burden of disease in vulnerable/at-risk populations. Specifically, pregnant and lactating women living with HIV may encounter the challenge of adequate food (including micronutrients) consumption, a weakened immune system, and the nutritional demands of a growing foetus or child.

In this review, four randomised controlled trials, conducted between 1995 and 2006, assessed the benefits of micronutrient supplementation. The trials took place in an urban setting in hospital-based antenatal clinics, with participants being pregnant women who ranged between 12-27 weeks of their pregnancy, and sample sizes ranging from 400 to 1129 participants. Multiple micronutrient supplements improved the health of pregnant women and their offspring. No significant adverse effects were reported. Zinc supplementation did not show any significant beneficial effects. Although it did not have any effect on the mother's pregnancy or her HIV disease, supplementation with selenium may increase the likelihood of a child surviving, and may reduce the likelihood of the mothers having diarrhoea. However, there is not enough evidence to determine the effect of micronutrient supplementation to pregnant women living with HIV who are being treated with antiretroviral medications.

Citation:

Siegfried N, Irlam JH, Visser ME, Rollins NN. Micronutrient supplementation in pregnant women with HIV infection. *Cochrane Database of Systematic Reviews* **2012**, Issue 3. Art. No.: CD009755. DOI: 10.1002/14651858.CD009755

Nutritional interventions for reducing morbidity and mortality in people with HIV

Adequate nutrition is important for optimal immune and metabolic function. Dietary support may, therefore, improve clinical outcomes in HIV-infected individuals by reducing the incidence of HIV-associated complications and attenuating progression of HIV disease, improving quality of life and ultimately reducing disease-related mortality.

Summary:

Achieving and maintaining optimal nutrition is considered an important adjunct in the clinical care of patients infected with HIV, as good nutrition can improve an individual's immune function, limit disease-specific complications, and improve quality of life and survival. We sought to determine whether macronutrient interventions, either given to provide protein and/or energy or test the effect of specific macronutrients (i.e. such as amino acids, whey protein concentrate or Spirulina), given orally, influence morbidity and mortality in adults and children living with HIV infection. Our review, based on fourteen small trials, evaluating different macronutrient supplements, found limited evidence that balanced macronutrient formulas increase protein and energy intake. However, we found no evidence that such supplementation translates into reductions in disease progression or HIV-related complications, such as opportunistic infections or death.

Citation:

Grobler L, Siegfried N, Visser ME, Mahlangu SSN, Volmink J. Nutritional interventions for reducing morbidity and mortality in people with HIV. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD004536. DOI: 10.1002/14651858.CD004536.pub3

Decentralising HIV treatment in lower- and middle-income countries

Policy makers, health staff and communities recognise that health services in lower- and middle-income countries need to improve people's access to HIV treatment and retention to treatment programmes. One strategy is to move antiretroviral delivery from hospitals to more peripheral health facilities or even beyond health facilities. This could increase the number of people with access to care, improve health outcomes, and enhance retention in treatment programmes. On the other hand, providing care at less sophisticated levels in the health service or at community-level may decrease quality of care and result in worse health outcomes. To address these uncertainties, we summarised the research studies examining the risks and benefits of decentralising antiretroviral therapy service delivery.

Summary:

Many people living with HIV who need antiretroviral therapy are unable to access or remain in care. This is often because of the time and cost required to travel to health centres. One approach to facilitating access and retention in care is to provide antiretroviral therapy close to people's homes, 'decentralising' treatment from hospitals to health centres or even to the community. We wanted to assess whether decentralisation of antiretroviral therapy reduced the number of people lost to follow-up. Because loss to follow-up in HIV programmes is known to include some people who have died, our main outcome of interest was 'attrition', which is the number of people who have either died or been lost to follow-up.

Study characteristics

We searched for studies up to March 2013. We found 16 studies, including two high quality randomised controlled trials and 14 studies collecting data from HIV care programmes. All but one study was conducted in Africa. The study participants included both adults and children who were followed-up for up to two years.

We describe three types of care:

- Partial decentralisation: starting antiretroviral therapy at the hospital, then moving to a health centre to continue treatment
- Full decentralisation: starting and continuing treatment at a health centre
- Providing antiretroviral therapy in the community: antiretroviral therapy is started at a health centre or hospital and thereafter provided in the community

Key results

We found that if antiretroviral therapy was started at a hospital and continued in a health centre (partial decentralisation), there was probably less attrition and fewer patients were lost to care after one year (four studies, 39 090 patients).

Where antiretroviral therapy was started and continued at a health centre (full decentralisation), there was probably no difference in the number of deaths and patients lost to follow-up (attrition), but overall, there were probably fewer patients lost to care after one year (four studies, 56 360 patients).

If antiretroviral therapy was provided in the community, by trained volunteers, there was probably no difference detected in death or losses to care when compared to care provided at a health centre after one year (two studies, 1 453 patients).

Overall, none of the models of decentralisation led to worse health outcomes. The research indicates that fewer patients are lost to care when they are continued on antiretroviral therapy at health centres rather than in hospitals. The research also did not detect a difference in the numbers of patients lost to care when they are treated in the community rather than in a health facility.

Citation:

Kredo T, Ford N, Adeniyi FB, Garner P. Decentralising HIV treatment in lower- and middle-income countries. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD009987. DOI: 10.1002/14651858.CD009987.pub2

Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy

The high levels of healthcare worker shortage is recognised as a severe impediment to increasing patients' access to antiretroviral therapy. This is particularly of concern where the burden of disease is greatest and the access to trained doctors is limited. This review aims to better inform HIV care programmes that are currently underway, and those planned, by assessing if task-shifting care from doctors to non-doctors provides both high quality and safe care for all patients requiring antiretroviral treatment.

Summary:

High levels of healthcare worker shortage has limited HIV infected patients access to antiretroviral therapy in lower and middle-income countries. This occurs most where the burden of HIV disease is greatest and where access to trained doctors is limited. We wanted to assess if task shifting of care from doctors to non-doctors provides both high quality and safe care for all patients requiring antiretroviral treatment.

Study characteristics

We searched for studies up to March 2014. We found 10 studies, including four randomised controlled trials and 6 cohort studies collecting data from HIV care programmes. All the studies were conducted in Africa in adults who were followed up for up to one year.

We describe three types of care:

- Doctor versus nurse or clinical officer care for initiation and maintenance of antiretrovirals
- Doctor versus nurse or clinical officer care for maintenance of antiretroviral therapy
- Doctor versus community health workers for maintenance of antiretroviral therapy.

Key results

We found high quality evidence from trial data that when nurses initiated and provided follow-up HIV therapy, there was no difference in death and lower rates of losses to follow up at one year, (2770 participants). However, lower quality data from two cohort studies suggests that there may be an increased risk of death in the task shifting group, (39 160 participants) but no difference in patients lost to follow-up between groups, We found moderate quality evidence from two trials that when doctors initiated therapy and nurses provided follow-up, that there was probably no difference in death or number

of patients lost to follow up at one year (4332 participants). Lower quality evidence from the cohort study showed that death as well as the number of patients lost to follow-up at one year may be lower in the group treated by nurses.

Compared to doctor led care, we found moderate quality evidence from a single trial that when antiretroviral therapy was provided in the community, by trained field workers, there was probably no difference in death or losses to follow-up (559 participants).

Citation:

Kredo T, Adeniyi FB, Bateganya M, Pienaar ED. Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy. *Cochrane Database of Systematic Reviews* **2014**, Issue 7. Art. No.: CD007331. DOI: 10.1002/14651858.CD007331.pub3

Integration of HIV/AIDS services with maternal, neonatal and child health, nutrition, and family planning services

The integration of HIV/AIDS and maternal, neonatal, child health and nutrition services (MNCHN), including family planning (FP) is recognised as a key strategy to reduce maternal and child mortality and control the HIV/AIDS epidemic. However, limited evidence exists on the effectiveness of service integration.

Summary:

Integrating HIV/AIDS prevention and treatment services with services focused on the health of mothers, infants and children, as well as on nutrition and family planning (MNCHN-FP) may improve the health of mothers and children affected by HIV/AIDS or a risk of HIV infection. We identified 20 studies representing 19 strategies for integrating these kinds of services. Overall, we found that integrating HIV/AIDS and MNCHN-FP services was feasible across a variety of integration models, locations, and populations. Most studies reported that integration had a positive impact on health outcomes. Many studies, however, also reported that some outcomes had improved, while others had not improved; or that there was no effect at all.

There are still significant gaps in the evidence. There is a need for rigorous research comparing the outcomes of integrated services with those of non-integrated services. Such studies should look at the impact of integrated programs on cost, cost-effectiveness, the rate at which new HIV and other sexually transmitted infections occur in the population, and the impact on the rate of serious illness and death in women and children. These rigorous studies will help researchers and doctors to develop effective integrated programs, and will help policy-makers to develop evidence-based health policy.

Citation:

Lindegren ML, Kennedy CE, Bain-Brickley D, Azman H, Creanga AA, Butler LM, Spaulding AB, Horvath T, Kennedy GE. Integration of HIV/AIDS services with maternal, neonatal and child health, nutrition, and family planning services. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD010119. DOI: 10.1002/14651858.CD010119

Integrating prevention of mother-to-child HIV transmission (PMTCT) programmes with other health services for preventing HIV infection and improving HIV outcomes in developing countries

Every year nearly 400,000 children are infected with HIV through mother-to-child transmission (MTCT), which is responsible for more than 90% of HIV infections in children. In high-income countries, the MTCT rate is less than 1% through perinatal prevention of mother-to-child HIV transmission (PMTCT) interventions. In low- and middle-income countries, PMTCT programme coverage remains low and consequently transmission rate high. The World Health Organisation recommends integration of PMTCT programmes with other healthcare services to increase access and improve uptake of these interventions.

Summary:

Ninety per cent of HIV infections in children under the age of 15 are a consequence of mother-to-child transmission of HIV during pregnancy, delivery and breastfeeding. In high-income countries introduction of prevention of mother-to-child HIV transmission (PMTCT) programmes reduced the rate of transmission of HIV from mothers to infants to 1%. These programmes consist of HIV testing, antiretroviral prophylaxis or therapy, safe obstetric practices and infant feeding counselling. PMTCT programmes have been implemented in low- and middle-income countries with variable success. One of the World Health Organization's proposed strategies to increase the coverage and quality of PMTCT programmes is to provide them within other healthcare services used by pregnant women, mothers and children: e.g. maternal and child health care services. We assessed the effectiveness of integrated PMTCT programmes compared to non-integrated and partially integrated care. We defined effectiveness as increased PMTCT programme uptake. We searched a number of databases for relevant studies. From the initial list of 28,654 references, only one study met the inclusion criteria. This study was conducted in 12 antenatal clinics in Zambia. Six intervention clinics implemented HIV testing of women of unknown serostatus and assessment of antiretroviral prophylaxis adherence of HIV positive women. In six control clinics, HIV testing was not performed at labour ward and HIV positive women were informally asked if they took antiretroviral prophylaxis. In all 12 clinics, women were provided with antiretroviral prophylaxis at labour ward if found to be HIV positive and non-adherent to antiretroviral prophylaxis. All children born to HIV positive women were also given antiretroviral prophylaxis. A significant increase in proportion of women and children receiving antiretroviral prophylaxis was observed in the clinics that implemented

the PMTCT interventions (of HIV testing and assessment of adherence to antiretroviral prophylaxis) compared to the control clinics. Women and children were more likely to receive antiretroviral prophylaxis at labour wards in the intervention clinics compared to control clinics. Although this one study showed that integrated care improved nevirapine coverage of women and infants more than non-integrated care, the paucity of evidence to confirm or refute this finding more widely suggests more research is urgently needed in other settings to allow a definitive conclusion about the effectiveness of integration of PMTCT interventions with other health services.

Citation:

Tudor Car L, van-Velthoven MHMMT, Brusamento S, Elmoniry H, Car J, Majeed A, Atun R. Integrating prevention of mother-to-child HIV transmission (PMTCT) programmes with other health services for preventing HIV infection and improving HIV outcomes in developing countries. *Cochrane Database of Systematic Reviews* **2011**, Issue 6. Art. No.: CD008741. DOI: 10.1002/14651858.CD008741.pub2

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