

HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV

ANNEX 3: Systematic review – HTC for adolescents

HIV testing and counselling (HTC) for preventing HIV transmission and improving uptake of HIV care and treatment in adolescents

Background

More than 34 million people are presently living with HIV. In 2009, there were more than 7000 new HIV infections each day worldwide (UNAIDS 2010a). Around 2500 of these new cases were in adolescents and young adults aged 15-24. Additionally, while most of the approximately 1000 new cases of HIV each day in children under 15 were caused by perinatal transmission, a small percentage were the result of early sexual debut (UNAIDS 2010b). Adolescents and young people remain extremely vulnerable to acquiring HIV infection, especially those who live in settings with a generalised HIV epidemic, or who are members of populations at high risk for HIV acquisition or transmission.

HIV testing and counselling (HTC) is an essential component of efforts to achieve universal access to HIV prevention, treatment, care and support. Young people who learn that they have HIV infection can learn to reduce the risk of transmitting HIV to others, as well as to obtain HIV treatment and care. Early access to care can help them to feel better and to live longer than if they were to present for care when their disease is already at an advanced stage. HIV testing and counselling can serve as a means for adolescents and young people to be diagnosed and to receive care and treatment as early as possible.

Objectives

The objectives of this systematic review are to provide a summary of the key evidence, along with practice and implementation recommendations, on effective or promising HTC interventions for improving uptake of HIV treatment, care and other services in adolescents. It will also identify gaps and prioritise areas where further research is required.

Methods

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)
- Non-randomised controlled trials
- Pre- / post-intervention evaluations
- Observational studies (e.g. cohort studies)

Types of participants

- Adolescents living in countries with a generalised HIV epidemic (HIV prevalence >1% among women attending antenatal clinics)
- Adolescents living in countries with a concentrated HIV epidemic (HIV prevalence >5% among subpopulations but <1% in the general population)

- Key populations of adolescents (e.g. drug users, sex workers, transgender persons, youth with male sex partners of any age, and other populations at higher risk of acquiring or transmitting HIV infection than the general population)

We define adolescents as individuals 10-19 years of age. For the purposes of the systematic review, we excluded studies that included both adolescents and adults, unless the data were stratified by age and could be disaggregated. As evidence was sparse, however, we included non-stratified studies (and even studies of only adults) in the GRADE evidence profiles. The quality of evidence from the literature of mixed or adult-only studies was downgraded, as appropriate, for indirectness.

Types of interventions

- HIV testing and counselling (HTC)
- HIV testing (without counselling)
- HIV counseling (without testing)

Types of outcome measures

Primary outcomes

1. Change in HIV incidence
2. Change in HIV mortality
3. Change in HIV morbidity
4. Change in STI incidence

Secondary outcomes

1. Access to and uptake of health care services
 1. HIV care and treatment
 2. Uptake of and adherence to antiretroviral therapy
 3. Sexually transmitted infections screening and treatment
 4. Tuberculosis screening, treatment and completion
 5. Hepatitis screening and treatment
2. Access to and uptake of prevention services
 1. Provision of condoms
 2. Male circumcision
 3. Prevention of mother-to-child HIV transmission
 4. Drug services
 5. Other relevant measures
3. Behaviour change
 1. Increased condom use
 2. Reduced sexual risk behaviour
 3. Delayed sexual debut
4. Psychosocial impact
 1. Reduction in mental health symptoms
 2. Reduction in stigma and discrimination
 3. Increased psychosocial support
 4. Improved quality of life

Search methods for identification of studies

See search methods used in reviews by the Cochrane Collaborative Review Group on HIV Infection and AIDS.

Electronic searches

We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress). Full details of the Cochrane HIV/AIDS Review Group methods and the journals hand-searched are published in the section on Collaborative Review Groups in The Cochrane Library.

Journal and trial databases

We searched the following electronic databases, in the period from 01 January 1985 (the year in which the first HIV antibody test was licensed in the United States) to the search date (1 October 2011):

- CENTRAL (Cochrane Central Register of Controlled Trials)
- EMBASE
- PsycINFO
- PubMed
- Web of Science / Web of Social Science
- World Health Organization (WHO) Global Health Library (www.globalhealthlibrary.net), which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO)

Along with appropriate MeSH terms and relevant keywords, we used the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE ([Higgins 2008](#)), and the Cochrane HIV/AIDS Group's validated strategies for identifying references relevant to HIV infection and AIDS. The search strategy was iterative, in that references of included studies were searched for additional references. All languages were included.

See [Appendix 1](#) for our PubMed search strategy, which was modified and adapted as needed for use in the other databases.

Searching other resources

Conference databases

We searched the Aegis archive of HIV/AIDS conference abstracts, which includes abstracts for the following conferences:

- British HIV/AIDS Association, 2001-2010
- Conference on Retroviruses and Opportunistic Infections (CROI), 1994-2008
- European AIDS Society Conference, 2001 and 2003
- International AIDS Society, International AIDS Conference (IAC), 1985-2006
- International AIDS Society, Conference on HIV Pathogenesis, Treatment and Prevention (IAS), 2001-2005
- US National HIV Prevention Conference, 1999, 2003, and 2005

We also searched the CROI and International AIDS Society web sites for abstracts presented at conferences subsequent to those listed above (CROI, 2009-2011; IAC, 2008-2010; IAS, 2007-2011).

Other resources

In addition to searching electronic databases, we contacted individual researchers, experts working in the field and authors of major trials to address whether any relevant manuscripts were in preparation or in press. The references of published articles found in the above databases were searched for additional pertinent materials.

We searched WHO's International Clinical Trials Registry Platform (ICTRP) to identify ongoing trials.

Data collection and analysis

Two authors (GWR and MLL) independently extracted data into a standardised, pre-piloted data extraction form. To the extent possible, the following characteristics were extracted from each included study:

- Administrative details: trial identification number; author(s); published or unpublished; year of publication; number of studies included in paper; year(s) in which study was conducted; details of other relevant papers cited;
- Details of the study: study design; type, duration and completeness of follow up; location/orientation of study (e.g. higher-income vs. low or middle-income country; stage of HIV epidemic)
- Details of participants: age range; gender, sexual or gender orientation if appropriate; clinical characteristics if appropriate
- Details of intervention: venue; qualifications of counselling personnel; characteristics of HIV diagnostic tests (e.g. rapid vs. standard)
- Details of outcomes
- Details necessary for risk of bias assessment

Risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the bias assessment tool described in the Cochrane Handbook ([Higgins 2008](#)). The Cochrane approach assesses risk of bias in individual studies across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases.

Sequence generation (checking for selection bias)

- Low risk: investigators described a random component in the sequence generation process, such as the use of random number table, coin tossing, card or envelope shuffling.
- High risk: investigators described a non-random component in the sequence generation process, such as the use of odd or even date of birth, algorithm based on the day or date of birth, hospital or clinic record number.
- Unclear risk: insufficient information to permit judgment of the sequence generation process.

Allocation concealment (checking for selection bias)

- Low risk: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; or sequentially numbered, opaque, sealed envelopes).

- High risk: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule, a list of random numbers), or envelopes were unsealed, non-opaque or not sequentially numbered.
- Unclear risk: insufficient information to permit judgment of the allocation concealment or the method not described.

Blinding (checking for performance bias and detection bias)

- Low risk: blinding of the participants, key study personnel and outcome assessor and unlikely that the blinding could have been broken. Not blinding in the situation where non-blinding is unlikely to introduce bias.
- High risk: no blinding or incomplete blinding when the outcome is likely to be influenced by lack of blinding.
- Unclear risk: insufficient information to permit judgment of adequacy or otherwise of the blinding.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome or missing outcome data balanced in number across groups.
- High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data.
- Unclear risk: insufficient reporting of attrition or exclusions.

Selective reporting

- Low risk: a protocol is available which clearly states the primary outcome is the same as in the final trial report.
- High risk: the primary outcome differs between the protocol and final trial report.
- Unclear risk: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.

Other forms of bias

- Low risk: there is no evidence of bias from other sources.
- High risk: there is potential bias present from other sources (e.g., early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).
- Unclear risk: insufficient information to permit judgment of adequacy or otherwise of other forms of bias.

The quality of evidence across the body of evidence was assessed with the GRADE approach ([Guyatt 2008](#)), which defines the quality of evidence for each outcome as “the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest” ([Higgins 2008](#)). The quality rating across studies has four levels: high, moderate, low or very low. Randomised trials are considered to be of high quality, but can be downgraded for any of five reasons; similarly, observational studies are considered to be of low quality, but can be upgraded for any of 3 reasons. The 5 factors that decrease the quality of evidence are 1) limitations in study design; 2) indirectness of

evidence; 3) unexplained heterogeneity or inconsistency of results; 4) imprecision of results; or 5). high probability of publication bias. The three factors that can increase the quality level of a body of evidence are 1) large magnitude of effect; 2) if all plausible confounding would reduce a demonstrated effect; and 3) if there is a dose-response gradient.

Observational studies were assessed for risk of bias using the above criteria, as well as other measures including the Newcastle-Ottawa Quality Assessment Scale ([Wells 2011](#)). Specifically, the scale uses a star system to judge three general areas: selection of study groups, comparability of groups, and ascertainment of outcomes (in the case of cohort studies). As a result, this instrument can assess the quality of non-randomised studies so that they can be used in a meta-analysis or systematic review.

Assessment of Quality of Evidence across Studies

We assessed the quality of evidence across a body of evidence (i.e., multiple studies with similar interventions and outcomes) with the GRADE approach ([Guyatt 2008](#)), defining the quality of evidence for each outcome as “the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest” ([Higgins 2008](#)). The quality rating across studies has four levels: high, moderate, low or very low. Randomised controlled trials are categorised as high quality but can be downgraded; similarly, other types of controlled trials and observational studies are categorised as low quality but can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results or high probability of publication bias. Factors that can increase the quality level of a body of evidence include a large magnitude of effect, if all plausible confounding would lead to an underestimation of effect and if there is a dose-response gradient

Measures of effect

We used Review Manager 5 provided by the Cochrane Collaboration for statistical analysis and GRADEpro software (GRADEpro 2008) to produce GRADE evidence profiles. We summarized dichotomous outcomes for effect in terms of risk ratio (RR), Odds ratio (OR), and Hazards ratio (HR) with their 95% confidence intervals. We present finding in GRADE evidence profiles for all outcomes of interest.

Results

Description of studies

Results of the search

Searches were conducted on 1 October, 2011, and produced 282 titles after 6 duplicates were removed. After initial screening of titles by TH, 99 titles and abstracts were selected for further review by two authors (GWR and MLL). GWR and MLL independently conducted the selection of potentially relevant studies by scanning the titles, abstracts, and descriptor terms of all downloaded material from the electronic searches. Irrelevant reports were discarded, and the full article was obtained for all potentially relevant or uncertain reports. GWR and MLL independently applied the inclusion criteria. TH acted as arbiter where there was disagreement. Studies were reviewed for relevance, based on study design, types of participants, types of interventions and outcome measures. Fifteen full-text articles were closely examined by two authors (GWR and MLL). We thus identified 5 randomised controlled trials and 5 observational studies that met our inclusion criteria for data extraction, coding and analysis.

Included Studies:

We identified five randomized controlled trials (Apoola 2011, Bolu 2004, Muhamadi 2011, Coates 2000, Wanyenze 2011) and four observational studies (Gwadz 2010, Kabiru 2010, Muller 1995, Naughton 2011) that met our inclusion criteria. The five RCTs were conducted in six countries. Three studies were conducted in countries with generalized HIV epidemics, including Uganda (Muhamadi 2011, Wanyenze 2011), Kenya, Tanzania, and Trinidad (Coates 2000). Two RCTs were conducted in concentrated or low level HIV epidemic settings among key populations of youth in STD clinics in the United States (Bolu 2004), and youth in substance misuse services in the United Kingdom (Apoola 2010). Five observational studies were conducted in four countries. Two observational studies were conducted in countries with generalized HIV epidemics including Kenya (Kabiru 2010) and South Africa (Naughton 2011). Two observational studies were conducted in concentrated or low level HIV epidemics, one in Thailand (Muller 1995) and one in the United States among key populations of homeless youth (Gwadz 2010).

Randomized controlled studies in generalized epidemic settings

Muhamadi 2011: This randomized, controlled trial was conducted in three health facilities in Eastern Uganda. Eligible participants were newly screened and identified HIV-positive clients from voluntary testing and counseling (VCT) at the three health facilities who were 18 years and older and not part of the PMTCT program. From July 2009 to June 2010, 400 participants were randomized to either standard of care where posttest counseling was delivered by staff not trained in basic counseling or the intervention arm consisting of specialized counseling delivered by staff with training in basic counseling skills and combined with home visits by community support agents for extended counseling and support. The primary outcome was the proportion of newly detected and counseled persons living with HIV (PLHIV) who had received pre-ARV care in the subsequent three months (+2 months). Uptake of pre-ARV care was significantly higher among HIV-positive patients who received the intervention compared to standard of care post-test counseling (RR 1.75, 95%CI 1.44 to 2.14). Additionally, among those who came for pre-ARV care, the majority of patients in the intervention arm (64.5%) compared to the control arm (34.5%) had disclosed their HIV status to their family.

Coates for the Voluntary HIV-1 Counseling and Testing Efficacy Group 2000: This randomized controlled trial was conducted in three sites in Nairobi, Kenya, Dar es Salaam, Tanzania, and Port of Spain, Trinidad. Eligible participants were 18 years and older and were not known to be infected with HIV. From 1995-1998, 3120 individuals were randomized to either voluntary counseling and testing, based on the US CDC client-centered HIV-1 counseling model or provision of standard health information. The VCT model includes personalized risk assessment and development of a personalized risk reduction plan for each client. At first follow-up, all health-information participants were offered VCT and all VCT participants were offered retesting. Primary outcomes were unprotected intercourse with primary and non-primary partners and STI incidence at six month follow-up. Unprotected sexual intercourse with a non-primary partner was significantly reduced among both men (RR 0.74, 95% CI 0.6 to 0.91) and women (RR 0.72, 95% CI 0.56 to 0.93) who received VCT compared to those who received basic health information only. STI incidence decreased (non-statistically significant) among those individuals who received VCT compared to standard health information (OR 0.80, 95% CI 0.53 to 1.20).

Wanyenze 2011: This randomized controlled trial was conducted at one site in Kampala, Uganda. Eligible participants were hospitalized in-patients who were over 18 years of age with unknown HIV

status. Exclusion criteria included those with altered mental status and those too ill to provide informed consent or to be interviewed. From March 2004 to March 2005, 3120 individuals were randomized to either free immediate inpatient HIV voluntary counseling and testing, based on the US CDC client-centered HIV-1 counseling model or referral for free outpatient HIV counseling and testing post-discharge. The VCT model includes personalized risk assessment and development of a personalized risk reduction plan for each client. Those randomized to the control group were given a referral card and an appointment to return for counseling and testing one week after discharge to the same hospital. Primary outcomes were linkage to medical care, including ARVs, and mortality at six months follow-up. Fewer HIV-positive patients in the intervention arm attended a HIV clinic compared to the control arm (RR 0.76, 95% CI 0.59 to 0.98). Fewer hospitalized HIV-positive adults who received VCT as inpatients were still alive compared to HIV-positive patients referred for VCT post-discharge (RR 0.83, 95% CI 0.68 to 1.0). Of note, 69% (171/249) in the control group (VCT referral post discharge) and 3/251(1%) in the inpatient intervention group were not tested for HIV.

Observational Studies in Generalized Epidemic Settings

Kabiru 2010: Kabiru and colleagues analyzed cross sectional, population-based data collected on a sample of youth aged 18-24 years from June to July 2007 in Kisumu Kenya. Information was collected from a 10-year retrospective life history calendar, including HIV testing since age 14 until the survey, capturing most of the HIV counseling and testing history. Outcomes included evaluating the impact of having an HIV test in the previous 6 months on subsequent sexual behavior, specifically concurrent sexual partnerships, unprotected sex in any partnership, or risky sexual partnerships (defined as partnership with a casual partner, commercial sex worker or client, one night stand or stranger) in a given month. Results were analyzed separately by sex and for females based on pregnancy status at first test.

Males who reported having an HIV test in past 6 months were significantly more likely to report concurrent sexual partnerships in a given month (HR 3.18, 95% CI 1.51 to 6.72) and having had a “risky” sexual partner in the past 6 months (non-statistically significant) (HR 1.11, 95% CI 0.61 to 2.01) compared to men who did not report HIV testing. Fewer men who had an HIV test in the past six months (non-statistically significant) reported having had unprotected sex (HR 0.98, 95% CI 0.75 to 1.28). However, males with greater number of cumulative HIV tests were significantly less likely to report concurrent sexual partnerships (0.57, 95% CI 0.40, 0.82). Among “ever pregnant” women, those having had an HIV test in the past 6 months were significantly less likely to have had unprotected sex in any given month, (HR 0.59, 95% CI 0.47 to 0.75) than those women who did not test. Though not-statistically significant, more “ever pregnant” women who had an HIV test in past 6 months reported having had a “risky” sexual partner (HR 1.18, 95% CI 0.33 to 4.16) and concurrent sexual partnerships (HR 1.67, 95% CI 0.51 to 5.48) compared to women who did not test. Among “never pregnant” women, having an HIV test in the past 6 month was significantly more likely to have had a “risky” sexual partner (HR 3.54, 95% CI 1.48 to 8.45) and (non-statistically significant) of unprotected sex in any given month (HR 1.64, 95% CI 0.94 to 2.83) compared to women who did not test. However, fewer “never pregnant” women (non-statistically significant) who had an HIV test in the past 6 months reported concurrent sexual partnerships (HR 0.69, 95% CI 0.07 to 7.12).

Naughton: 2011 Naughton and colleagues reported data in an abstract from a retrospective case series among children >12 years old attending schools in Mbhasa district, Eastern Cape, South Africa. Voluntary counseling and testing teams visited 12 schools between June 2008 and August 2009 to establish HIV education and counselling programs which included group education on HIV, individual counselling for HIV testing, and Point of Care (POC) HIV testing. Follow-up attempts were made by trained lay counselors to enroll those that tested HIV positive into local HIV wellness program. Retrospective analysis of the program was conducted with follow-up period of 2-14 months. Of 758 adolescents tested for HIV, 7(0.9%) tested positive. However, none (0%) of the 7 HIV-positive adolescents identified subsequently attended the clinic for care. There was no control group, and the relative effect was not calculable.

Randomized controlled studies in low-level epidemic settings or among key populations

Bolu 2004: Bolu and colleagues conducted a subgroup analysis of a randomized, controlled trial of HIV counseling efficacy (Project RESPECT) conducted in 5 public STD clinics in the United States. Eligible participants were 14 years old and older, English-speaking, who reported vaginal intercourse within preceding 3 months. Male-male sex within past 12 months was exclusion criterion. From July 1993 to September 1996, 4328 participants were randomized to four intervention arms with varying intensity of safer-sex counseling with trained HIV counselor or clinician, arm 1: enhanced counselling (1 20-minute counselling session + 3 1-hour sessions with counselor); arm 2: brief prevention counselling (1 20-minute counseling session + 1 20-minute session 7-10 days later-based on CDC's client-centered HIV counseling) or Arm 3: HIV prevention education (one 5-minute session with clinician + one 5-minute results reporting session). The subgroup analysis included 14-20 year old participants (N=764) in the trial in first three arms that followed participants up to 12 months. Primary outcome was STI incidence, based on laboratory diagnosis during the 12 months after the intervention. *Neisseria gonorrhoeae* was diagnosed by culture or urethral swab Gram stain, *Chlamydia trachomatis* by endocervical PCR or urine, and syphilis by treponemal and non-treponemal tests, and HIV. STI incidence was decreased in adolescents in the HIV counseling interventions (brief or enhanced) (17.3%) compared to those in the educational messages group (26.6%) (RR 0.65, 95% CI 0.49 to 0.86). The efficacy of brief counseling was similar to enhanced counseling.

Apoola 2011: This randomized controlled trial was conducted in the UK. Eligible participants were 13 to 19 years of age attending young person's substance misuse service who were deemed competent to participate. From 2007 to 2008, 54 participants were randomized to either pre-test discussion with immediate oral swab for HIV, HBV and HCV, with results available in two days, and appointment at STI clinic for genital infection screening (N=27) or pre-test discussion counseling with referral to the STI clinic for same day blood testing for HIV (also offered testing for syphilis, hepatitis B and C and genital infection screening) (N=27). Primary outcome was attending STI screening at STI clinic and secondary outcomes included number receiving results within a week of testing, and number receiving at least one dose or all three doses of HBV and Hepatitis A vaccination. With 1 week follow-up, attendance at STI clinic for STI screening increased in adolescents undergoing oral swab HIV testing (33%) vs. those offered referral for blood HIV testing (11%), though not statistically significant (RR 3, 95% CI 0.91 to 9.88). Uptake of HIV, HBV, and HCV testing increased in the immediate oral swab compared to referral group (RR 8.77, 95% CI 4.73 to 16.26) but there was no difference in receipt of all 3 doses of HAV and HBV vaccines (RR 0.90, 95% CI 0.43 to 1.85).

Observational studies in low-level epidemic settings or among key populations

Gwadz 2010: Gwadz et al conducted a cross sectional study of 217 homeless youth, ages 15-24 years, who were recruited through respondent driven sampling in New York City in 2007-2008. The objective was to compare practices and the context of rapid and conventional HIV testing among this population and to examine the extent of referrals and linkages to services post HIV testing. Outcomes were referral or linkage to care including medical care, mental health, HIV prevention services, homeless shelter or other community services after the last rapid or conventional HIV test. Most of the youth had been tested for HIV in the past year (82%), and had received pre- and posttest counseling (77%) for both rapid and conventional tests. Overall, only 44% received referral to or linkage to health and/or community services after testing. More patients received referrals and linkages following a conventional test (35%) than following a rapid test (26%) ($p=.092$)

Muller 1995: Muller and colleagues conducted a cross sectional study among 300 HIV-positive consecutive patients attending the immune clinic in Bangkok, Thailand about their HIV testing history, sexual behavior, including number of sexual partners and condom use, after receipt of their positive HIV test result. These self-report data were compared to similar data collected among 300 consecutive age- and gender-matched controls attending the anonymous VCT clinic before voluntary counseling and testing. With a median of 23 months follow-up, adolescents and adults in the intervention group (after VCT) were significantly more likely to report condom use during the last 3 episodes of sexual intercourse, compared to controls (RR 3.78, 95% CI 2.65 to 5.39) and to report having had fewer sexual partners ($N=0-1$) in the past six months compared to controls (RR 1.82, 95% CI 1.53 to 2.15). This was largely due to the difference in those reporting no sexual partner (42% vs 14%).

Excluded studies

We excluded four studies after reviewing the full text articles (and in one case the conference abstract). Mollen 2008, and Sattin 2011 were excluded because they did not include a comparison. Tolou-Shams 2007 was excluded because the intervention was designed to improve testing rates. Woods 2002 was excluded because there was no comparison between tested and not tested (the study combined HIV-negative and untested).

Risk of Bias in included studies

Effects of Interventions

Using Cochrane Collaboration methods, we performed a systematic review.

Should HIV testing and counselling be used for HIV prevention and linkage to care among adolescents in generalised epidemic settings?

In generalized epidemic settings, three randomized controlled trials examined the efficacy of HIV counseling and testing among participants who were 18 years of age and older (Coates 2000, Muhamadi 2011, Wanyenze 2011). There were no trials that examined HIV testing and counselling specifically among adolescents less than 18 years of age. Each of these trials examined different study populations,

interventions, and outcomes and, therefore, could not be combined into a meta-analysis. One RCT examined the efficacy of CDC's client-centered HIV counseling compared to standard health information among participants who were not known to be HIV-infected on the incidence of laboratory confirmed STIs and self-reported unprotected sexual intercourse (Coates 2000). Another trial compared an enhanced post-test counseling intervention with community support to standard post-test counseling among newly screened HIV-positive patients on uptake of pre-ARV care (Muhamadi 2011) in Uganda. The third trial compared immediate inpatient HIV client-centered HIV-1 counseling and testing to referral for outpatient HCT post-discharge among hospitalized patients in Uganda on attendance at HIV clinic and survival six month post-discharge for those who tested HIV-positive (Wanyenze 2011). There were two observational studies that included adolescents in the study population (Naughton 2011, Kabiru 2010), one presented as an abstract only (Naughton 2011). Results for these observational studies are presented separately.

Randomized controlled trials

One randomized, controlled, multi-site trial examined the efficacy of voluntary HIV counseling and testing, based on the US CDC client-centered HIV-1 counseling model, compared to provision of standard health information among adolescent and adult populations 18 years of age and older who were not known to be HIV-infected (Coates 2000). The study included participants from three countries (Kenya, Tanzania, and Trinidad). Unprotected sexual intercourse with a non-primary partner was significantly reduced among both men (RR 0.74, 95% CI 0.6 to 0.91) and women (RR 0.72, 95% CI 0.56 to 0.93) who received VCT compared to those who received basic health information at six months follow-up. STI incidence decreased (non-statistically significant) among those individuals who received VCT compared to standard health information (OR 0.80, 95% CI 0.53 to 1.20).

In an RCT addressing an enhanced post-test counseling intervention compared to standard of care among newly identified HIV-positive patients, uptake of pre-ARV care was significantly higher among HIV-positive patients who received the intervention, consisting of enhanced post-test counseling by trained staff combined with home visits by community support agents for extended counseling) compared to standard of care post-test counseling (RR 1.75, 95%CI 1.44 to 2.14) (Muhamadi 2011).

In an RCT that examined the effectiveness of an inpatient HIV testing intervention compared to referral for HIV after discharge (control) , fewer HIV-positive patients in the intervention arm attended an HIV clinic at six months follow-up compared to those who received referral for VCT post-discharge (RR 0.76, 95% CI 0.59 to 0.98) (Wanyenze 2011). Fewer hospitalized HIV-positive patients who received VCT as inpatients were still alive at six months compared to those referred (RR 0.83, 95% CI 0.68 to 1.0). However, 69% of those in the control group (VCT referral post discharge) were not tested for HIV compared to only 1% in the intervention arm.

There were no trials that examined the efficacy of HIV counseling and testing on the health outcomes of HIV incidence or morbidity, quality of life, stigma, or TB or hepatitis screening and treatment.

Observational Studies

Two observational studies of very low quality were identified that included adolescents <18 years in the study population. Evidence from these two studies found mixed results compared to the indirect evidence from RCTs among adults. HIV testing among adolescents did not result in safer sexual behaviors for all subpopulations nor increased enrollment in HIV care for those identified as positive. In

one observational study (Kabiru 2010) with 6 months follow-up, males who reported having an HIV test in past 6 months were significantly more likely to report concurrent sexual partnerships in a given month (HR 3.18, 95% CI 1.51 to 6.72), and significantly more “never pregnant” women who had an HIV test in past 6 months reported having had a “risky” sexual partner in the past 6 months, compared to women in the control group (HR 3.54, 95% CI 1.48 to 8.45). Though among “ever pregnant” women, those having had an HIV test in the past 6 months were significantly less likely to have had unprotected sex in any given month, (HR 0.59, 95% CI 0.47 to 0.75) than those women who did not test. The other observational study of very low quality (Naughton 2011) was a retrospective analysis, with no control group, of the impact of an HIV education, counselling and point of care HIV testing program conducted in schools. Despite follow-up attempts made by trained lay counselors, none (0%) of the seven adolescents identified as HIV positive enrolled in the HIV wellness program

Should HIV testing and counselling be used for HIV prevention and linkage to care among key populations of adolescents in concentrated/low-level epidemic setting?

Among key populations of adolescents in concentrated/low level epidemic settings, two randomized controlled trials examined the efficacy of HIV counseling and testing among adolescent populations (Bolu 2004, Apoola 2011). One conducted a subgroup analysis of 14-20 year old participants (N=764) from a larger HIV prevention counseling trial in the United States (Bolu 2004), and another was conducted among 13 to 19 years of age attending young person’s substance misuse service in the UK (Apoola 2011). Each of these trials examined different study populations, interventions, and outcomes and, therefore, could not be combined into a meta-analysis. One RCT examined the efficacy of HIV counseling (Project RESPECT) interventions of varying intensities of one-on-one safer sex counseling with a trained HIV counselor conducted in STD clinics. Both enhanced counseling and brief prevention counseling were compared to HIV prevention education on the incidence of STDs at 12 months follow-up (Bolu 2004). The other trial evaluated the efficacy of pre-test discussion with immediate oral swab for HIV, HBV and HCV testing and appointment at STI clinic for genital infection screening or pre-test discussion counseling with referral to the STI clinic for same day blood testing for HIV on uptake of HIV, HCV, and HBV testing, HAV and HBV vaccination, and attendance at the STI clinic. (Apoola 2011). There were no trials that examined the outcomes of change in HIV incidence, HIV morbidity and mortality, linkage to HIV care, access to and uptake of prevention services, behavior change or psychosocial impact.

There were two observational studies (Gwadz 2010, Muller 1995). One included homeless youth 15 to 24 years of age (Gwadz 2010) in the United States, and one included a non-stratified mixed adult/adolescent population in HIV and VCT clinics in Thailand (Muller 1995). Results for these studies are presented separately.

Randomized controlled trials

Data from a subgroup analysis of adolescents in an RCT of HIV counseling efficacy (Project RESPECT) (Bolu 2004) demonstrated that HIV prevention counseling (brief or enhanced) resulted in fewer STDs for adolescents compared to those who received HIV educational messages (RR 0.65, 95% CI 0.49 to 0.86), with brief interactive counseling (CDC client-centered HIV prevention counseling model) having similar efficacy to enhanced counseling in reducing new STDs.

In the other RCT (Apoola 2011) with 1 week follow-up, uptake of HIV, HBV, and HCV testing increased significantly in adolescents engaging in substance misuse services who had immediate oral swab HIV testing compared to those offered referral for blood testing (RR 8.77, 95% CI 4.73 to 16.26) but there was no difference in receipt of all 3 doses of HAV and HBV vaccines (RR 0.90, 95% CI 0.43 to 1.85). Attendance at STI clinic increased (non statistically significant) in those with oral swab HIV testing vs. those referred for blood testing (RR 3, 95% CI 0.91 to 9.88).

Observational Studies

In one observational study providing very low quality evidence (Gwadz 2010) 26% of HIV-positive adolescents subsequently attended clinic for care, while 35% in the control group attended clinic. In the second observational study of very low quality (Müller 1995), adolescents in the intervention group (after VCT) were significantly more likely to report having had fewer sexual partners (N=0-1) in the past six months (RR 1.82, 95% CI 1.53 to 2.15) and significantly more likely to report condom use during the last 3 episodes of sexual intercourse (RR 3.78, 95% CI 2.65 to 5.39) compared to controls.

Discussion

Summary of main results

We found few randomized controlled trials examining the impact of HIV testing among adolescents and young adults in either generalized epidemic settings or high-risk populations in low level epidemics on patient important outcomes.

In generalized epidemic settings, there are no randomized trials conducted specifically among adolescent populations. However, indirect evidence from RCTs conducted among adults found that HIV counseling and testing is effective at reducing unprotected sexual intercourse with non- primary partners and STI incidence among those at risk for HIV infection. Additionally, enhanced post-test counseling that includes community support agents is effective at improving uptake of pre-ARV care among HIV positive patients. Observational studies, despite including the target population of adolescents were of very low quality and evidence was mixed concerning the impact of HIV testing on sexual risk taking behaviors or uptake of HIV care.

Data from RCTs and high quality observational data are needed about the efficacy of HIV testing in adolescent populations on HIV incidence, morbidity and mortality as well as uptake of services and risk behaviors in generalized epidemic settings. Applicability of the current evidence among adults to adolescent populations is not known. With new evidence to support treatment as prevention and impact of potent antiretroviral regimens on reductions in HIV related morbidity and mortality, more data are needed on impact of different HIV counseling and testing strategies for reducing HIV incidence and improve linkage to HIV care for adolescents that are HIV-infected. Most data on effectiveness are based on the CDC VCT model, which includes personalized risk assessment and development of a personalized risk reduction plan for each client. The impact of more brief discussions with HIV testing needs further evaluation among adolescent populations. Furthermore, data are needed on most cost-effective strategies for testing adolescent populations, whether in facilities, prevention services, or in the community and effective strategies to link those that test positive to HIV care and treatment.

In low level epidemic settings among high risk youth where general population HIV prevalence rates are much lower than in Sub-Saharan Africa, data from sub analysis of one RCT demonstrate the effectiveness of HIV counseling and testing in reducing the incidence of STDs among heterosexual adolescents attending STD clinics. This interactive, risk-reduction counseling that includes personalized risk assessment and risk-reduction plans has not been studied in all high-risk populations, including young men who have sex with men or homeless and substance-abusing youth where more data are needed. Though this model has also demonstrated effectiveness in generalized epidemic settings among adults, the applicability of these data to adolescents in low level epidemic settings is unclear where there may be a need for specialized counseling due to higher risk behaviors, lack of HIV knowledge, and community outreach approaches. Data from another RCT among youth in substance abuse services support the use of community testing using rapid, oral, point-of-care technologies in improving uptake of HIV, HBV, and HCV testing and may provide a unique model for high risk populations. No studies evaluated the impact of HIV testing among adolescent populations in low level epidemics on HIV incidence, morbidity and mortality. More data are needed among young men who have sex with men and other high risk groups on efficacy of HIV counseling and testing interventions on patient important outcomes and linkage to care.

Quality of evidence

GRADE

In the GRADE system, well-conducted randomized controlled trials, without additional imitations, provide high quality evidence, and observational studies, without any additional strengths or limitations, provide low-quality evidence. The quality of evidence provided by a body of literature comprised of observational studies would be graded as low.

In this analysis, we found that the quality of evidence among RCTs varied from very low to moderate in generalized epidemic settings and low to very low in low level epidemics. Quality of evidence was moderate for the outcome of STI incidence based on one RCT (Coates 2000), which was downgraded only for indirectness due to a largely adult population. However, for all other outcomes in both generalized and low-level epidemics, evidence from RCTs was either of low or very-low quality, downgraded for imprecision (few participant and events) and indirectness (evidence from largely adult populations, or self-reported behavioral outcomes). Additionally, one study was also downgraded for indirectness as the population was sick, hospitalized inpatients (Wanyenze 2011).

In this analysis, we found that the quality of evidence among the observational studies was very low, downgraded for serious study design limitations (no comparator), imprecision (few participants and events), and indirectness (self-reported behavioral outcomes or evidence from largely adult populations).

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