WHO/HIV/2013.134

ANNEX 9: Review methods

Our methodology in conducting the systematic reviews was based on the guidance of the Cochrane Handbook for Systematic Reviews of Interventions .[1]

General inclusion criteria

To be included in the respective systematic reviews and GRADE analyses, an article had to meet the following criteria:

1) Published in a peer-reviewed journal, or presented as a peer-reviewed abstract at a scientific meeting.
2) Include outcome data for an intervention that is pertinent to at least one PICO question of interest.
3) Eligible study designs included randomised controlled trials (RCT), non-randomised controlled trials, pre-post-intervention evaluations, and other observational studies (e.g. cohort studies) with comparators.

Specific inclusion criteria for each review

1. Should HIV testing and counseling (HTC) be offered to adolescents?

Population:

- 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)

Interventions:

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

Comparator

- No HTC

Outcomes:

- Change in HIV incidence
- Change in HIV mortality
- Change in HIV morbidity
- Change in STI incidence

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

2. Can training of health workers in adolescent health improve retention and adherence among adolescents living with HIV?

Population:

- Adolescents (males and females) 10-19 years old.

Intervention:

- Training of health workers who provide care and treatment to adolescents living with HIV.

Comparator:

- No training of health workers in adolescent health.

Outcomes:

- Mortality
- Morbidity
- Proportion of appointments kept
- Continuation rates for medications/commodities

3. Should adolescents disclose their HIV status to parents, family members, sexual partners, others?

In view of the expected paucity of evidence from studies conducted in adolescents, studies conducted in adults were eligible for inclusion in the first instance.

Population:

- Adolescents (males and females) 10-19 years old.

Intervention:

- Disclosure of HIV status to
    - Parents

- Family members
- Sexual partners
- Friends
- Others

Comparator:

- No disclosure.

Outcomes:

- Reduced mortality among adolescents
- Reduced morbidity among adolescents
- Improved quality of life
- Reduced HIV transmission to sexual partners
- Proportion of patients on ART with suppressed viral load at 3, 6, 12, 24 months
- Proportion of patients maintained on 1st line therapy
- Proportion of patients 'adhering' by standard adherence measure
- Proportion of appointments kept
- Continuation rates for medications/commodities
- Proportion of adolescents using condoms with sexual partner/s
- Proportion of adolescents with depression, mental health problems, or proportion of adolescents who rate good on QoL assessment measures)

4. What is the best way to support adolescents to disclose their HIV status safely and effectively?

In view of the expected paucity of evidence from studies conducted in adolescents, studies conducted in adults were eligible for inclusion in the first instance.

Population:

- Adolescents (males and females) 10-19 years old.

Intervention:

- Support for disclosure by counsellor, health worker, peers

Comparator:

- No support for disclosure.

Outcomes:

- Reduced mortality among adolescents
- Reduced morbidity among adolescents
- Improved quality of life
- Reduced HIV transmission to sexual partners
- Proportion of patients on ART with suppressed viral load at 3, 6, 12, 24 months
- Proportion of patients maintained on 1st line therapy
- Proportion of patients 'adhering' by standard adherence measure
- Proportion of appointments kept
- Continuation rates for medications/commodities
- Proportion of adolescents using condoms with sexual partner/s
- Proportion of adolescents with depression, mental health problems, or proportion of adolescents who rate good on QoL assessment measures)

5. Can community-based approaches improve adherence to treatment and retention to care among adolescents?

Population:

- Adolescents (males and females) 10-19 years old.

Intervention:

- Community-based initiatives involving the provision of health services or support by informal caregivers or peers in the home or other community settings including preventive, promotive, therapeutic, rehabilitative or palliative care. Examples include home visits or support groups led by non-professional health workers (e.g., community health workers, lay health workers, volunteer health workers, church volunteers, etc.), peers, or other community members.

Comparator:

- No activities at the community level.

Outcomes:

- Mortality
- Morbidity
- Proportion of patients on ART with suppressed viral load at 3, 6, 12, 24 months
- Proportion of patients maintained on 1st line therapy
- Proportion of patients adhering by standard adherence measure
- Proportion of appointments kept
- Continuation rates for medications/commodities

Search methods and screening process

We searched PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, Web of Science, and WHO's Global Index Medicus. Along with Medical Subject Heading (MeSH) terms and relevant keywords, we used the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials, augmented with terms for capturing reports of observational studies, and the Cochrane HIV/AIDS Group's existing strategies for identifying references relevant to HIV/AIDS. The search strategies were iterative, in that references of included studies were searched for additional references. All languages were included. Our core PubMed search strategies were modified as needed for use in the other databases. See Tables 1-4 below.

Using a variety of relevant terms, we also searched the clinical trials registry at the WHO International Clinical Trials Registry Platform, which includes trials from many countries including all trials listed in "ClinicalTrials.gov."

We searched the online abstract archives of relevant conference proceedings, including the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS). These conferences were searched from their inception dates (1993, 1985, and 2001 respectively) to the most recent conference (2012, 2012 and 2011, respectively). We contacted individual researchers working in the field in an attempt to learn of any research we had not identified.

In each review, after removal of duplicate references and an initial screening by one author to remove clearly irrelevant references, two authors working independently then reviewed the titles, abstracts and descriptor terms of the remaining citations to identify potentially eligible reports. We obtained full text articles for all references identified as potentially meeting inclusion criteria. Two authors reviewed these

full text articles and applied the inclusion criteria to establish each study's eligibility or ineligibility. Studies were reviewed for relevance based on study design, intervention given, types of participants and outcome measures. See Tables 5-8 below.

Data collection and analysis

In each review, after identifying studies for inclusion, two authors working independently examined and extracted data from each study. Two authors separately entered these data into standardised data extraction forms. Extracted data in the forms were then compared. A neutral arbiter stood by in the event of any disagreement or discrepancy.

Extracted data included: Study details, participant details, intervention details, outcome details, and details necessary to assess the risk of bias (in the case of RCTs) or to assess study quality (in the case of observational studies).

In the case of RCTs, we assessed the risk of bias with the Cochrane collaboration's tool.[1] In the case of observational studies, we assessed study quality with a 9-point rigor scale[2-11] developed by the Johns Hopkins-WHO Synthesizing Intervention Effectiveness Project.

Measures of treatment effect

We used Review Manager 5.2 provided by the Cochrane Collaboration for preparing the review and for statistical analysis. We summarised dichotomous outcomes for effect using risk ratios (RR), with 95% confidence intervals (CI). We calculated summary statistics using meta-analytic methods and present findings in regard to evidence quality in GRADE summary of findings tables, for all outcomes of interest.

Assessment of heterogeneity

We examined heterogeneity between the trials using the I^2 statistic. We interpreted an I^2 estimate greater than 50% as indicating moderate or high levels of heterogeneity.

Data synthesis

When study populations, interventions, comparators and outcomes were sufficiently similar, we pooled the data across studies and estimated summary effect sizes using a fixed effect model if there was little heterogeneity between the trials, or a random effects model if there were moderate or high levels. We summarised the quality of evidence provided using GRADE evidence profiles.

Assessment of evidence quality by outcome

We graded the quality of evidence for each outcome using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach.[12] We used the GRADEpro software, version 3.2, to perform our analyses.

GRADE ranks the quality of evidence on four levels: "high," "moderate," "low" and "very low." Evidence from randomised controlled trials starts at "high," but can be downgraded based on study limitations, inconsistency of results, indirectness of evidence, imprecision or for reporting bias. Evidence from observational studies starts at "low," but can be upgraded if the magnitude of treatment effect is very large, if there is a significant dose-response relation, or if all possible confounders would decrease the magnitude of an apparent treatment effect. Evidence from observational studies can also be downgraded.

Tables 1-4: Core PubMed search strategies (modified as needed for use in the other databases)

Search	Table 1: PubMed strategy: Adolescent HTC (1 Jan 1985 – 23 October 2012)
#4	Search (((#1) AND #2) AND #3)
#3	counsel*[ti] OR test*[ti] OR HTC[tiab] OR HCT[tiab] OR VCT[tiab] OR PITC[tiab] OR PICT[tiab] OR voluntary[tiab] OR (link*[tiab] OR refer*[tiab]) AND care[tiab]) OR Counseling/methods[mh] OR Counseling/utilization[mh] OR AIDS Serodiagnosis[mh] OR Referral and Consultation[mh] OR Patient Acceptance of Health Care[mh]
#2	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR random* [tw] OR research design [mh:noexp] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) OR non-randomi*[tw] OR nonrandomi*[tw] OR "before after"[tw] OR "before and after"[tw] OR "time series"[tw] OR longitud*[tw] OR cohort*[tw] OR observational[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh OR evaluat*[tiab] NOT (animals [mh] NOT human [mh])
#1	HIV Infections[mh] OR HIV[mh] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) OR Sexually Transmitted Diseases[mh] OR "sexually transmitted"[tiab]

Search	Table 2: PubMed strategy: Provider training (1 Jan 1980 – 22 May 2012)
#9	Search (#7) OR #8
#8	Search ((#3) AND #4) AND #6
#7	Search (((#3) AND #4) AND #5) AND #6
#6	Search (Health Services Accessibility[mh] OR Clinical Competence/standards[mh] OR Health Services Needs and Demand[mh] OR Health Services Research[mh] OR Health Knowledge, Attitudes, Practice[mh] OR Primary Health Care/standards[mh] OR Physician's Practice Patterns/standards[mh] OR Continuity of Patient Care/organization & administration[mh] OR ((Specializ*[tiab] OR specialis*[tiab]) AND care[tiab]) OR Specialization[mh] OR Education, Medical[mh] OR Quality Improvement[Mesh] OR continuing education[tiab] OR (provider[tiab] AND train*[tiab])) AND (experience[tiab] OR skill[tiab] OR competenc*[tiab] OR satisfact*[tiab] OR knowledge[tiab] OR needs[tiab] OR consult*[tiab] OR Patient Satisfaction[mh]) AND (provider[tiab] OR professional[tiab] OR physician*[tiab] OR nurs*[tiab] or clinician*[tiab] OR practitioner*[tiab])
#5	Search (adolescen*[tiab] OR teen*[tiab] OR youth[tiab] OR young people[tiab] OR juvenile*[tiab]) AND (care[tiab] OR service*[tiab]))) OR youth-friendly[tiab] OR Adolescent Health Services [Mesh]

#4	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [MeSH] OR random allocation [MeSH] OR double-blind method [MeSH] OR single-blind method [MeSH] OR clinical trial [pt] OR clinical trials [MeSH] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [MeSH] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR follow-up studies [MeSH] OR prospective studies [MeSH] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) OR non-randomi*[tw] OR before after study[tw] OR time series[tw] OR case control[tw] OR prospective cohort[tw] OR retrospective cohort[tw] OR cross-section*[tw] OR prospective[tw] OR retrospective[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR prospective studies[MeSH] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals [MeSH] NOT human [MeSH])
#3	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab]))

Search	**Table 3: PubMed strategy: Disclosure (1 Jan 1980 – 14 August 2012)**
#5	Search (((#1) AND #2) AND #3) AND #4
#4	"Disclosure"[mh] OR "Self Disclosure"[mh] OR "Truth Disclosure"[mh] OR disclos*[tw] OR non-disclos*[tw] OR nondisclos*[tw] OR "truth telling"[tiab] OR (truth[tiab] AND tell*[tiab]) OR ("bad news"[tiab] AND (partner*[tiab] OR couple*[tiab] OR parents[tiab] OR friend*[tiab] OR family[tiab]))
#3	HIV Seropositivity/diagnosis[mh] OR sero-positive[tiab] OR seropositive[tiab] OR status[tiab] OR sero-status[tiab] OR serostatus[tiab] OR serodiscordant[tiab] OR sero-discordant[tiab] OR discordant[tiab] OR HIV-positive[tiab] OR "test result*"[tiab]
#2	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR random* [tw] OR research design [mh:noexp] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) OR non-randomi*[tw] OR nonrandomi*[tw] OR "before after"[tw] OR "before and after"[tw] OR "time series"[tw] OR longitud*[tw] OR cohort*[tw] OR observational[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh OR evaluat*[tiab] NOT (animals [mh] NOT human [mh])

#1	HIV Infections[mh] OR HIV[mh] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) OR Sexually Transmitted Diseases[mh] OR "sexually transmitted"[tiab]

Search	**Table 4: PubMed strategy: Community-based approaches (1 Jan 1999 – 17 Sept 2012)**
#5	Search (((#1) AND #2) AND #3) AND #4
#4	Search HIV Infections[mh] OR HIV[mh] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab]))
#3	Search randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv* [tw] OR volunteer*[tw]) OR non-randomi*[tw] OR nonrandomi*[tw] OR (before[tiab] AND after[tiab)] OR "before and after"[tw] OR "time series"[tw] OR longitud*[tw] OR cohort*[tw] OR observational[tw] OR prospective*[tw] NOT (animals [mh] NOT human [mh])
#2	Search "Patient Compliance"[mh] OR adheren*[tiab] OR retention[tiab] OR (suppress*[tiab] AND "viral load"[tiab])
#1	Search "lay health worker"[tiab] OR LHW*[tiab] OR "community caregiver*"[tiab] OR CCG[tiab] OR "Community-based"[tiab] OR CBAS[tiab] OR "Community engagement"[tiab] OR "Community mobilization"[tiab] OR "Community mobilisation"[tiab] OR (Community[tiab] AND particip*[tiab]) OR "Treatment support worker*"[tiab] OR TSW[tiab] OR "treatment mobilizer*"[tiab] OR "treatment mobilizer*" OR (Community[tiab] AND “health worker*”[tiab]) OR CHW[tiab] OR Accompagnateur*[tiab] OR buddies[tiab] OR buddy[tiab] OR "school-based"[tiab] OR school*[tiab] OR (Community[tiab] AND psychosocial[tiab]) OR (Community[tiab] AND home-based[tiab]) OR (Community[tiab] AND “service delivery”[tiab]) OR "Patient advocate*"[tiab] OR Kheth’Impilo[tiab] OR "Community Health Workers"[mh] OR "Peer Group"[mh]) OR "Social Support"[mh]

Tables 5-8: Screening processes for each review

Table 5: Screening process: Adolescent HTC	
Total of records	636
Duplicates removed	17
Records screened	619

Records excluded	589
Full-text articles obtained	33
Studies included in review	11

Table 6: Screening process: Provider training	
Total of records	1471
Duplicates removed	395
Records screened	1076
Records excluded	1035
Full-text articles obtained	41
Studies included in review	4
Studies actually meeting inclusion criteria	0

Table 7: Screening process: Disclosure (both questions)	
Total of records	2701
Duplicates removed	239
Records screened	2462
Records excluded	2362
Full-text articles obtained	100
Studies included in review ("Should adolescents disclose?")	30
Studies included in review ("What is the best way?")	16

Table 8: Screening process: Community-based approaches	
Total of records	656
Duplicates removed	116
Records screened	540
Records excluded	461
Full-text articles obtained	79
Studies included in review	27

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