Integracija programa za prevenciju prijenosa HIV-a s majke na dijete s drugim zdravstvenim službama u svrhu sprječavanja HIV infekcije te poboljšanja ishoda nakon HIV infekcije u zemljama u razvoju

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Split, 2012.

The Cochrane Collaboration
The Cochrane Library
2011, svezak 6

Voditelj rada: Lorainne Tudor Car, dr.med.
Naziv institucije gdje je rad izrađen: Medicinski fakultet Sveučilišta u Splitu i Imperial College, London

Srdačno se zahvaljujem doc. dr. sc. Ozrenu Polašek dr. med. mom dodijeljenom mentoru, dragoj profesorici dr. sc. Ani Marušić, dr. med., te profesoru dr. sc. Rifatu Atunu direktoru centra za međunarodni zdravstveni menadžment, Sveučilišta Imperial, London, na svesrdnoj pomoći prilikom izrade ove doktorske disertacije.

Osobita mi je čast harno se zahvaliti prof. dr. Azeemu Majeedu, predstojniku Odjela za primarnu zdravstvenu zaštitu i javno zdravstvo Sveučilišta Imperial u Londonu, UK koji je nesebično brojnim poticajnim sugestijama i korisnim savjetima pridonio završetku rada.

Posebnu zahvalnost želim izraziti mojoj dragoj obitelji, osobito ocu Mariju i majci Neli, na potpori, savjetima i povjerenju u toku cijelog mog školovanja.

SADRŽAJ

Popis oznaka i kratica

ART - antiretrovirusna terapija, eng. *antiretroviral therapy*

ARV - antiretrovirusna, eng. *antiretroviral*

CCT - kontrolirano kliničko istraživanje, eng. *controlled clinical trial*

GGE - jednadžbe generalizirane procjene (eng. *generalized estimating equations)*

HIV - virus humane imunodeficijencije

PMTCT - prevencija prijenosa s majke na dijete, eng. *prevention of mother to child transmission of HIV*

RCT - randomizirano kontrolirano istraživanje, eng. *randomised controlled trial*

SZO - Svjetska zdravstvena organizacija (WHO)

UVOD

Dosadašnje znanje

Žene u generativnoj dobi (od 15. do 44. godine) čine 50% populacije zaražene (Human Immunodeficiency virus) HIV-om u Subsaharskoj Africi (1). Kopnica je vodeći uzrok smrti među ženama generativne dobi. Svjetska zdravstvena organizacija (SZO) procjenjuje da se svakog dana HIV virusom zarazi 1000 djece mlađe od 15 godina. Preko 90% HIV infekcija u djece mlađe od 15 godina nastaje uslijed prijenosa HIV-a s majke na dijete. Više od 90% prijenosa HIV infekcije s majke na dijete nastaje u Subsaharskoj Africi (1). U zemljama u razvoju, bez provedenih mjera prevencije, rizik prijenosa HIV-a s majke na dijete je između 15% i 40%; od toga se 5% - 10% dogodi tijekom trudnoće, 10% - 20% u toku porođaja, a 5% - 20% dojenjem (2). U razvijenim je zemljama ta stopa smanjena na približno 1% zahvaljujući posebnim mjerama prevencije prijenosa HIV-a s majke na dijete (na eng. *prevention of mother-to-child transmission of HIV* ili PMTCT).

PMTCT programi se prema SZO dijele u četiri kategorije:

1) mjere sprječavanja primarne HIV infekcije u žena,
2) prevencija neželjenih trudnoća kod HIV pozitivnih žena,
3) sprječavanje prijenosa HIV infekcije s trudnica i dojilja na njihovu djecu te
4) njega i potpora ženama, novorođenčadi i obiteljima zaraženim HIV-om te onima oboljelima od side/kopnice (3).

Treća se skupina PMTCT intervencija sastoji se od testiranja trudnica na HIV, davanja antiretrovirusne (ARV) profilakse ili antiretrovirusne terapije (ART) ženama tijekom trudnoće ili porođaja te novorođenčadi nakon porođaja, zatim od posebnih mjera za sprječavanje prijenosa u toku poroda te konačno savjetovanju o ishrani novorođenčadi. Ove su se intervencije pokazale učinkovitima i isplativima u smanjivanju prijenosa HIV-a s majke na dijete (4-7). Ipak, jasni dokazi o učinkovitosti i isplativosti integracije PMTCT programa s drugim zdravstvenim službama nedostaju.

Na posebnoj sjednici Opće skupštine Ujedinjenih Naroda, održanoj 2001. godine, postavljen je cilj da se do 2010. godine udio HIV-om zaražene novorođenčadi smanji za 50%. Za postizanje tog cilja potrebno je da barem 80% trudnica i njihove djece dobije nužnu prevenciju i liječenje (8). U skladu s navedenim, globalno je financiranje HIV/AIDS

programa u nerazvijenim i srednje razvijenim zemljama povećalo s 1.6 milijardi američkih dolara u 2001. godini na 15.9 milijardi američkih dolara u 2009. godini. Usprkos značajnom porastu ulaganja sredstava za prevenciju HIV infekcija i za liječenje kopnice u zemljama u razvoju, spomenutom cilju Ujedinjenih Naroda te dokazanoj gospodarstvenoj učinkovitosti PMTCT programa, udio žena i djece u ovim programima ostaje i dalje neprihvatljivo nizak (1). U zemljama malog i srednjeg prihoda u 2009. godini, na HIV infekciju testirano je 26% trudnica, a 53% (40% - 79%) žena zaraženih HIV-om dobilo je barem nekakvu vrstu ARV profilakse. Svega je 15% (10% - 28%) novorođenčadi HIV pozitivnih majki bilo testirano na HIV (9). Obuhvaćenost PMTCT intervencijama bila je ispod 50% u 11 od 25 zemalja s najvećim udjelom žena koje trebaju primiti ARV profilaksu sa svrhom smanjenja prijenosa s majke na dijete (9). U brojnim se znanstvenim publikacijama i člancima usmjerenim na poboljšanje spomenutih programa (9-13), ističe jedna od glavnih preporuka - integracija PMTCT programa s drugim zdravstvenim službama i to uglavnom onim službama namijenjenim zdravstvenoj zaštiti žena i djece. Integracija ovih programa predstavlja ključnu strategiju za poboljšanje zdravlja te za preživljavanja žena i djece u zemljama s velikim HIV bremenom. Prvi su PMTCT programi u zemljama u razvoju bili pojedinačni/zasebni te su se tek postupno integrirali s onim službama koje su pružale zdravstvenu zaštitu majkama i novorođenčadi. Pravo opravdanje za integraciju PMTCT programa sa službama za zdravstvenu zaštitu majki i djece leži u činjenici da se brojne PMTCT intervencijske mjere provode baš tijekom trudnoće, potom porođaja te ranog postpartalnog vremenskog perioda. Nadalje, većina žena u zemljama u razvoju zatraži zdravstvenu skrb barem jednom u toku trudnoće (u zemljama s malim prihodom 69% trudnica, u zemljama nižeg-srednjeg prihoda 79% trudnica, a u zemljama višeg-srednjeg prihoda 94% trudnica). Na taj se način može doprijeti do žena i djece izloženih visokom riziku od HIV infekcije, ili već zaraženih HIV-om (12). No samo jedan pregled tijekom trudnoće ne omogućava primjenu svih PMTCT intervencija. Udio trudnica koje su imale barem četiri pregleda prije porođaja je mnogo niži (u zemljama malog prihoda 39%, u zemljama nižeg-srednjeg prihoda 47% i u zemljama višeg-srednjeg prihoda 75%. Ništa bolji nije ni udio trudnica koje su imale stručno-vođen porođaj (u zemljama malenog prihoda 43%, u zemljama nižeg-srednjeg prihoda 65%, a u zemljama višeg-srednjeg prihoda 95%).

Stoga se nameće zaključak da trudnice koje tijekom trudnoće i poroda uopće ne zatraže zdravstvenu zaštitu, neće niti biti obuhvaćene PMTCT programima integriranim s tim službama. Uz to, u PMTCT programima, bili oni integrirani ili ne, postoji stalan gubitak

sudionica između svake pojedine PMTCT intervencije: od prvog doticaja kroz savjetovanje, testiranje, obavijesti o rezultatima testiranja, primanja ARV profilakse ili ART-a, testiranja te liječenja novorođenčadi, preporuke za novorođenačku prehranu i postnatalno praćenje (9,17). Primjerice, u multinacionalnom PMTCT programu Pedijatrijske zaklade Elizabeth Glaser za borbu protiv kopnice, od 100 trudnica koje su zatražile antenatalnu zdravstvenu skrb, 92 su bile savjetovane, 77 ih je bilo testirano na HIV, a 69 je dobilo rezultate testova. Od osam HIV pozitivnih žena, šest je bilo primilo ARV profilaksu. Tek su četiri novorođena djeteta, HIV pozitivnih majki, bila primila ARV profilaksu.

Važnost PMTCT intervencija te njihove integracije npr. sa zdravstvenim službama za zaštitu majki i novorođenčadi postaje jasnija uzmemo li u obzir „feminizaciju“ HIV/AIDS pandemije (tj. veću ranjivost žena na HIV infekciju) (12). Žene su naime, tijekom nezaštićenog heteroseksualnog odnosa s HIV pozitivnim partnerom, izložene dvostruko većem riziku od infekcije HIV-om nego muškarci! Rizik dalje raste zbog neizjednačenosti prava između spolova, zbog siromaštva, neobrazovanosti te zbog spolnog zlostavljanja (18).

Značajan porast stope HIV-om zaražene djece, kao posljedice prijenosa HIV infekcije s majke na dijete, potakla je Glavnog tajnika pa i ključne službe Ujedinjenih Naroda da apeliraju na povećanje domaćeg i međunarodnog materijalnog ulaganja u zdravstvenu zaštitu žena i djece u zemljama u razvoju, da bi se dosegnuo četvrti i peti razvojni milenijski cilj (tj. smanjenje smrtnosti djece te poboljšanje zdravlja majki) te tako povećao udio sudionica u PMTCT programima (19).

Preliminarnim pretraživanjem literature pronašli smo jedan sustavni pregledni članak SZO iz 2008. godine usmjeren na integraciju spolne te reproduktivne zdravstvene zaštite s HIV programima (20). Ovaj sustavni pregled obuhvaća prve, druge i četvrte skupine PMTCT programa, dok je treća skupina PMTCT intervencija, isključena. Uz to smo pronašli i nekoliko nesustavnih pregleda literature (21-24).

Definicija integrirane zdravstvene skrbi

Postoji više definicija integrirane zdravstvene zaštite te isto tako brojni načini kako je zdravstvena zaštita u stvarnosti integrirana u zemljama u razvoju (25-28). U literaturi se razlikuju dva glavna koncepta integriranja zdravstvene skrbi:
a) ustrojstvo zdravstvene skrbi koje se temelji na gospodarstvenoj opravdanosti,
b) ustrojstvo zdravstvene skrbi utmeljeno na raznovrsnosti načina/razina pružanja iste (29).

Iako je integracija postupak koji se zbiva na raznim razinama zdravstvenog sustava (regionalni, županijski, zdravstvene ustanove/ambulante) i u svezi je s ključnim zdravstvenim funkcijama (tj. upravljanje, ulaganje, planiranje, pružanje zdravstvenih usluga, promatranje i procjenjivanje, izgrađivanje potražnje) (25), integracija u zdravstvene ustanove je (tj. na razini pružanja zdravstvene usluge) je ključna za sveobuhvatnost palete onih usluga koje se bolesnicima još pružaju (12). Jedna od glavnih odrednica uspjeha i moguće koristi integracije PMTCT programa s drugovrsnom zdravstvenom zaštitom je poboljšan pristup takvim ustanovama te olakšano korištenje zdravstvenih usluga (30, 31). Ovdje primarno procjenjujemo na koji način, integracija PMTCT programa u ostale zdravstvene službe, utječe kako na obuhvaćenost korisnika mjerama PMTCT intervencija tako i na samu primjenu (prihvaćenost) PMTCT programa. Stoga, integraciju PMTCT programa u druge zdravstvene službe, definiramo kao udruživanje pružanja specifične zdravstvene usluge bilo na pojedinačnom („sveobuhvatnom“) mjestu ili kao upućivanje iz jedne zdravstvene ustanove u drugu (20). Integrirane programe u kojima su se korisnici mjera PMTCT intervencija dodatno upućivali iz jedne zdravstvene ustanove u drugu (opskrkbljeniju), držimo tek djelomično integriranim.

Kako bi mjere intervencija mogle biti učinkovite?

Integracija PMTCT programa sa srodnim zdravstvenim službama može korisnicima olakšati pristup tim ustanovama te, sukladno tome, trudnicama/rodiljama i novorođenčadi omogućiti bolje korištenje tih mjera intervencija. Takva bi integracija mogla poboljšati kvalitetu antenatalne i majčinske skrbi, ne samo za korisnike koji primaju PMTCT usluge, nego za sve žene i njihovu djecu putem boljeg sinergističkog korištenja raspoloživih financijskih sredstava, podučavanjem zdravstvenih djelatnika, boljom evidencijom te procjenjivanjem učinkovitosti zdravstvene skrbi. Integracija sa zdravstvenim službama za majčinsku i novorođenačku skrb mogla bi djelovati poput katalizatora za uvrštavanje PMTCT programa u

druge zdravstvene službe koje se nude trudnicama, rodiljama, majkama i novorođenčadi; mogla bi pomoći u smanjenju stigmatizacije HIV pozitivnih žena (što je ključna prepreka za korištenje prevencije, testiranja i liječenja); te smanjiti paralelno provođenje istih zdravstvenih službi i suvišno natjecanje za i tako oskudna financijska sredstva. U zemljama u razvoju, bi se PMTCT programi mogli integrirati korištenjem postojećeg kadra te infrastrukture uz minimalno dodatno ulaganje sredstava, dovodeći na taj način do bolje iskoristivosti i tako oskudnih ljudskih i novčanih sredstava za zdravstvo (30, 32).

Ipak, integriranje novih zdravstvenih usluga moglo bi preopteretiti već i tako slabe zdravstvene sustave u zemljama u razvoju. Primjerice, integracija ranog testiranja novorođenčadi na HIV, unutar programa cijepljenja dojenčadi, znatno bi povećala radno opterećenje zdravstvenih djelatnika vodeći potencijalno slabijem pružanju zdravstvene skrbi (33). Manjak sredstava, rukovodećih kadrova i nekonzistentno medicinsko dokumentiranje mogu imati negativnog utjecaja na primjenjivost i održivost tih integriranih službi. Poduka o PMTCT programima može dovesti do odljeva mozgova zdravstvenih radnika u ante- ili perinatalnoj skrbi u druge, bolje opremljene programe (ustanove) za borbu protiv kopnice te na taj način smanjiti i tako oskudne kadrove. Posebne, odvojene sobe u integriranim PMTCT programima za HIV savjetovanje mogu ugroziti privatnost HIV pozitivnih žena, povećati stigmu (obilježenost) te odvratiti druge žene od korištenja službi integriranih s PMTCT programima. Osoblje bi moglo pokazivati nelagodu pri pružanju zdravstvene njege HIV-om zaraženih ili potencijalno zaraženih korisnika zdravstvene zaštite, što bi vodilo diskriminaciji te neprikladnoj kvaliteti zdravstvene zaštite (23,34). Pružanje ART-a u antenatalnim klinikama te usmjeravanje žena nakon poroda u zasebne HIV klinike za daljnje liječenje, moglo bi dovesti do gubitka brojnih sudionica iz sustava zdravstvene skrbi te prekida uzimanja ART (35).

Zašto je važno načiniti ovakav pregledni članak?

Pravodobnost ovog preglednog članka je očigledna uzimajući u obzir nedavno iskazanu predanost međunarodnih udruga ka poboljšanju PMTCT programa u nerazvijenim i srednje razvijenim zemljama. Glavni tajnik Ujedinjenih Naroda, države ćlanice „G8“ kluba i Globalna zaklada za borbu protiv kopnice, tuberkuloze i malarije, u suradnji s ključnim US službama (UNAIDS, SZO, UNICEF, UNFPA i CIFF) su posvetili svoje djelovanje daljnjem razvoju i poboljšanju kvalitete i učinkovitosti PMTCT programa u zemljama u razvoju (19,36). Integracija je PMTCT programa u druge, stručno povezane službe, glavna sastojnica

njihove strategije (37). Zanimljivo je istaknuti da sustavna procjena učinaka integracije PMTCT programa u ostale zdravstvene službe u zemljama u razvoju nije do sada uopće bila provedena. Imajući pred očima važnost ovog pitanja i nezadovoljavajuće dokaze, jasno je da postoji potreba za sustavnom procjenom učinkovitosti integriranih PMTCT programa. Ovaj će prikaz omogućiti korisne obavijesti sadašnjim i budućim korisnicima i stručnjacima koji donose planove razvoja u nastojanjima da se potakne povećanje udjela sudionica u PMTCT programima. Nadalje će doprinjeti prikladnijem usmjeravanju sredstava za pružanje PMTCT intervencija, na najbolji mogući način.

Ciljevi

Procijeniti učinke integracije perinatalnih PMTCT programa s ostalim zdravstvenim službama na udio trudnica, rodilja i novorođenčadi koje su primile PMTCT intervencije u usporedbi s tek pojedinačnim PMTCT programima ili pak onima, gdje je ta utkanost PMTCT programa s drugim zdravstvenim službama, tek djelomična. Pod drugim se zdravstvenim uslugama podrazumijevaju: zdravstvena skrb za majke, za novorođenčad i djecu HIV pozitivnih roditelja, zdravstvena skrb za osobe sa spolno prenosivim bolestima, zatim službe savjetovanja, službe testiranja na HIV itd.

METODE

Kriteriji odabira studija

Vrste studija

Preliminarnim smo pretraživanjem literature utvrdili postojanje tek malenog broja randomiziranih, kontroliranih studija (RCT) te smo također uključili i cluster randomizirane, kontrolirane studije, kontrolirane kliničke studije (CCT), studije „s nadzorom prije i poslije“ i studije „isprekidanih vremenskih nizova“. Prihvatljivim smo držali studije „nadzirane prije i poslije“ koje su istovremeno imale prikupljanje podataka usporedno prije i poslije intervencije te prikladnu kontrolu. Studije „isprekidanih vremenskih nizova“ morale su imati jasno definirano vrijeme provedbe intervencije te barem tri različita vremenska odsječka prikupljanja podataka prije i poslije intervencije.

Vrste sudionika

Uključili smo studije koje su usmjerene na trudnice i novorođenčad s nepoznatim HIV statusom (integracija testiranja majki i djece s ostalim službama) i HIV pozitivne trudnice i rodilje (integracija intervencija poput pružanja ARV profilakse ili ART-e, siguran porod te savjetovanje o ishrani novorođenčeta, s drugim službama) u zemljama u razvoju.
Zemlje u razvoju definirali smo u skladu s podjelom Svjetske banke na zemlje niskog prihoda, nižeg srednjeg prihoda te višeg srednjeg prihoda (38).

Vrste postupaka

Prema SZO se PMTCT programi dijele na četiri skupine (3). Naš je pregled usmjeren na treću skupinu PMTCT mjera tj. perinatalne PMTCT postupke. Ovaj paket specifičnih i učinkovitih PMTCT mjera za sprječavanje prijenosa s majke na dijete uključuje: 1) utvrđivanje HIV pozitivnog statusa kod trudnica; 2) pružanje ARV profilakse HIV pozitivnim majkama; 3) pružanje ART-e HIV pozitivnim majkama; 4) sprječavanje prijenosa HIV infekcije tijekom poroda kroz poboljšane opstetričke mjere; 5) savjetovanje HIV pozitivnih majki o prehrani novorođenčadi s ciljem smanjivanja prijenosa HIV infekcije; 6) pružanje ARV profilakse novorođenčadi; 7) ranu dijagnozu HIV pozitivnog statusa kod novorođenčadi. U ovaj smo sustavni pregled uključili sve studije usmjerene prema integraciji bilo kojih (uključivo i više od jednog) perinatalnih PMTCT postupaka s drugim zdravstvenim službama poput:
1) trudničkih predporođajnih dispanzera
2) stručne, porodničarske skrbi u ustanovi tijekom trajanja porođaja
3) poslijeporođajnu skrb
4) novorođenačku skrb
5) pedijatrijsku skrb
6) programe hranjenja
7) centre za testiranje na HIV i potporu HIV pozitivnim osobama
8) centre za liječenje HIV pozitivnih osoba
9) ginekološke službe
10) ustanove za spolno prenosive bolesti
11) centre za planiranje obitelji
12) primarnu zdravstvenu skrb
13) hitnu medicinsku pomoć
14) ustanove za tuberkulozu

15) ustanove za malariju
16) ustanove za cijepljenje
17) bilo koju drugu zdravstvenu službu.

Kontrolne mjere zaštite su uključivale uobičajenu zdravstvenu skrb, tj. neintegrirane zdravstvene službe (zasebni perinatalni PMTCT programi), ili djelomično integrirani PMTCT programi s bilo kojim drugim zdravstvenim službama. Djelomično integrirane PMTCT programe definirali smo kao one programe gdje su žene koje posjećuju zdravstvene ustanove bile upućivane dalje, u zasebne (druge) zdravstvene ustanove, da bi tek tamo primale PMTCT mjere zaštite.

Vrste mjera ishoda

Primarni ishodi

Učinkovitost PMTCT intervencija:
• udio HIV pozitivnih trudnica koje su primile ARV profilaksu ili ART
• udio trudnica upoznatih s PMTCT intervencijama
• udio trudnica testiranih na HIV, uključivo i one kojima je već prije trudnoće dokazan HIV
• udio trudnica zaraženih HIV-om koje su imale siguran porođaj bilo kod kuće ili u bolnici
• udio trudnica zaraženih HIV-om koje su savjetovane o prehrani novorođenčadi
• udio novorođenčadi HIV pozitivnih majki koja su primila ARV profilaksu
• udio novorođenčadi HIV pozitivnih majki testirane na HIV

Sekundarni ishodi

• postotak HIV negativne novorođenčadi od HIV pozitivnih majki
• (gospodarska) isplativost integriranih PMTCT programa
• učinak na zdravstveno osoblje
• prosječna kvaliteta zdravstvene skrbi
• učinak na stigmu (obilježenost) povezanu s HIV pozitivnim statusom (diskriminiranost)

Metode pretraživanja literature za pronalaženje relevantnih studija

Koristili smo sveobuhvatnu strategiju pretraživanja kako bismo pronašli svaku relevantnu studiju (primjer u Tablici 1).

Tablica 1. Strategija pretraživanja za MEDLINE (PubMed)

#1 Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral:noexp"[MH]
#2 Search mother-to-child[tiab] OR MTCT[tiab] OR mother-to-infant[tiab] OR adult-to-child[tiab] OR maternal-to-child[tiab] OR vertical transmission[tiab] OR perinatal transmission[tiab] OR postnatal transmission[tiab] OR post natal transmission[tiab] OR maternal-infant transmission[tiab] OR PMTCT[tiab] OR infectious disease transmission, vertical/prevention and control[mh]
#3 Search #4 AND #5
#4 Search (#4 AND #5) NOT (animals[mh] NOT humans[mh])
#5 Search (#4 AND #5) NOT (animals[mh] NOT humans[mh]) Limits: Publication Date from 1990/01/01 to 2010/07/26

Uključili smo studije na svim jezicima, ali sa sažetkom na engleskom jeziku. Ograničili smo pretraživanje na period poslije 1990. godine jer su te godine tek bili uvedeni prvi PMTCT programi (39). Koristili smo strategiju pretraživanja visoke osjetljivosti, koju je razvila Cochrane skupina za HIV/AIDS, a koja se sastoji od sljedećih pojmova:

mother to child transmission (prijevod: prijenos s majke na dijete) ili MTCT ili prevention of mother to child transmission (prijevod: prevencija prijenosa s majke na dijete) ili PMTCT ili disease transmission vertical (prijevod: vertikalan prijenos bolesti) ili perinatal transmission (prijevod: perinatalni prijenos bolesti) ili postnatal transmission (prijevod: prijenos bolesti nakon rođenja) ili maternal-infant transmission (prijevod: prijenos s majke na dijete) ili mother-to-infant transmission (prijevod: prijenos s majke na dijete).

Međunarodno dogovorena definicija integrirane zdravstvene zaštitite još nije utvrđena. Pojedini su autori, iako usmjereni na integriranu zdravstvenu zaštitu, u svojim radovima možda izostavili taj pojam ili su ga možebitno drugačije označili. Stoga naša strategija pretraživanja nije uključila pojmove povezane s integriranom zdravstvenom skrbi. Unatoč tome, u svakoj smo potencijalno relevantnoj studiji analizirali način organizacije zdravstvene zaštite te pokušali utvrditi je li ona u skladu s našom definicijom integrirane zdravstvene zaštite.

U ovaj smo sustavni pregledni nastojali uključiti sve objavljene studije usmjerene na integraciju PMTCT programa s drugovrsnom zdravstvenom zaštitom. Druga zdravstvena zaštita predstavlja niz raznovrsnih programa koji mogu imati čitavu paletu naziva. Vjerujemo da bismo, pri pokušaju uključivanja nazivlja u strategiju pretraživanja literature, smanjili osjetljivost pretraživanja.

Računalno (elektroničko) pretraživanje literature

Pretražili smo MEDLINE (od siječnja 1990. do srpnja 2010.), EMBASE od siječnja 1990. do srpnja 2010.), the Cochrane Database of Systematic Reviews (the Cochrane Library 2010, svezak 7), the Cochrane Central Register of Controlled Trials (the Cochrane Library 2010, svezak 7), Database of Abstracts of Reviews on Effects (the Cochrane Library 2010, svezak 7). The WHO Global Health Library (od siječnja 1990. do kolovoza 2010.), sažetke iz CAB (od siječnja 1990. do kolovoza 2010.), CINAHL (od siječnja 1990. do kolovoza 2010.), POPLINE (od siječnja 1990. do kolovoza 2010.), PsycINFO (od siječnja 1990. do kolovoza 2010.), Sociological Abstracts (od siječnja 1990. do kolovoza 2010.), ERIC (od siječnja 1990.

do kolovoza 2010.), i U.S. National Library of Medicine Gateway system (od siječnja 1990. do kolovoza 2010.).

Pretraživanje drugih izvora

Također smo pretražili literaturu relevantnih studija te proveli ISI Web of Knowledge „Cited Reference“ pretragu. Nismo uključivali potencijalno relevantna kongresna priopćenja ili sažetke u slučajevima kada nam nisu bile dostupne dodatne informacije. Pretražili smo WHO International Clinical Trials Registry (od siječnja 1990. do kolovoza 2010.) i Controlled clinical trials (od siječnja 1990. do kolovoza 2010.) s ciljem pronalaska relevantnih nedovršenih kliničkih istraživanja.

Pokušali smo pronaći neobjavljene studije pretraživanjem sive literature poput AEGIS (od siječnja 1990. do kolovoza 2010.), Google Scholar (od siječnja 1990. do kolovoza 2010.) New York Academy of Medicine Grey Literature (od siječnja 1990. do kolovoza 2010.), Open SIGLE (od siječnja 1990. do kolovoza 2010.), British Library Catalogue (od siječnja 1990. do kolovoza 2010.) i Pro Quest Dissertation & Theses Database (od siječnja 1990. do kolovoza 2010.). Pretraživanje Google Scholar rezultiralo je velikim brojem dobivenih navoda od kojih smo izabrali prvih 500.

Prikupljanje podataka i analiza

Izbor radova

Rezultate pretraživanja literature smo unijeli i pregledali u EndNote-u X4, računalnom programu za obradu literature. Dva su autora, neovisno jedan o drugome, pregledala naslove, sažetke i cijele tekstove potencijalno važnih studija. Autori su neslaganje o prikladnosti pojedinih studija za uključivanje u ovaj sustavni pregledni članak rješavali raspravom. Ako su i dalje bili neusuglašeni s obzirom na uvrštavanje izvjesne studije, treći autor je donosio odluku. Proces odabira studija prikazali smo pomoću adaptiranog *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* dijagrama (40).

Prikupljanje podataka i obrada

Podatke iz studija prikupljali smo koristeći standardizirane formulare koji su sadržavali ključne informacije iz članaka, kao što su administrativni podaci (naslov, autor, stadij objavljivanja članka, godina objavljivanja, zemlja u kojoj je studija provedena itd.), metode

(vrsta studije, podaci važni za procjenu rizika od sustavne pogreške, trajanje i potpunost praćenja bolesnika), informacije o sudionicima, intervencijama, ishodima, provedene usporedbe i druge primjedbe.

Podatke iz studija prikupljali su dva autora neovisno jedan o drugome. Autori su različitosti u prikupljenim podacima rješavali raspravom te zajedničkom odlukom. Kada se nisu mogli dogovoriti, treći je autor donosio odluku.

Procjenjivanje rizika od sustavne pogreške u uvrštenim studijama

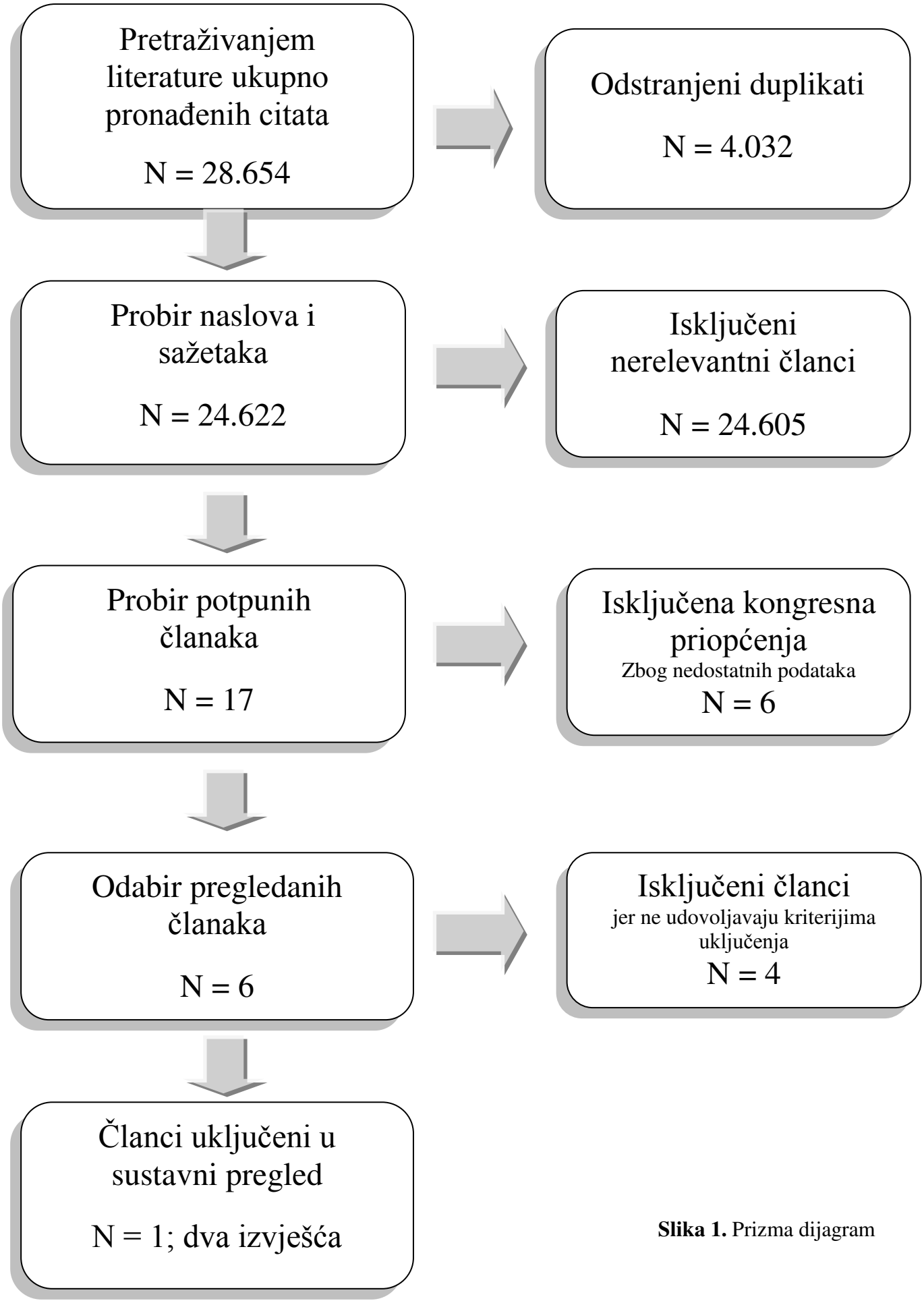
Dva su autora ovog članka neovisno jedan od drugome proveli početnu procjenu metodologije uključenih studija te su potencijalne različitosti u procjeni rješavali raspravom. Uvrštene studije smo analizirali koristeći „Risk of Bias" metodu, opisanu u udžbeniku *the Cochrane Handbook for Systematic Reviews of Interventions* te dodatne kriterije koje je razvila *the Cochrane Effective Practice and Organisation of Care (EPOC) Group* (41, 42). Za svaki kriterij donosili smo opisnu ocjenu poput: nizak rizik od sustavne pogreške, nesiguran rizik od sustavne pogreške ili visok rizik od sustavne pogreške. Nismo pronašli niti jednu relevantnu RCT, CCT, ili studiju „nadziranu prije i poslije" i studiju „isprekidanog vremenskog niza". Kod uvrštene relevantne cluster randomizirane studije, rizik od sustavne pogreške procjenjivali smo traženjem pogreške uvrštavanja sudionika, neujednačenosti karakteristika sudionika u različitim cluster-ima, gubljenjem cluster-a, pogrešne analize podataka i usporedivosti s individualnim RCT-om (41).

Postupak s nedostupnim podacima

Prikazali smo stopu odustajanja sudionika u uvrštenoj studiji. Nismo provodili nikakve dodatne analize ni proračune kod nepotpunih podataka u uvrštenoj studiji (35, 43).

REZULTATI

Pretraživanjem literature pronašli smo 28.654 potencijalno relevantnih referenci. Probirom naslova i sažetaka pronašli smo šest (35, 43-48) potencijalno relevantnih studija. Jedna studija imala je dva izvješća (47, 48). Uz to smo pronašli jednu potencijalno relevantnu nedovršenu studiju (49). Našli smo 11 potencijalno relevantnih kongresnih sažetaka za koje nismo mogli dobiti dodatne informacije, iako smo kontaktirali autore. PRISMA dijagram na Slici 1 prikazuje probir stud



Slika 1. Prizma dijagram

Uključene studije

Pronašli smo samo jednu relevantnu cluster randomiziranu studiju s dva izvješća u vidu članka i doktorske radnje (Tablica 2) (47, 48). Spomenuta je studija na engleskom jeziku. Provedena je u Lusaki, u Zambiji, u 12 klinika za porode od listopada 2005. do siječnja 2006. godine. U studiji je sudjelovalo 7664 žena koje su rađale u klinikama za porode. Šest klinika je randomizacijom svrstano u intervencijsku skupinu, a šest u kontrolnu skupinu. Zdravstvenu zaštitu u studiji pružale su primalje.

Tablica 2. Obilježja uključene studije

Metode	Cluster randomizirana kontrolirana studija provedena u Lusaki, Zambija u 12 klinika za porode od listopada 2005 do siječnja 2006 godine. Šest klinika randomizrano je u intervencijsku skupinu, a drugih šest u kontrolnu skupinu. U svim klinikama, zdravstvenu zaštitu su pružale primalje.
Sudionici	7664 rodilja u spomenutim klinikama za porode.
Intervencije	**Intervencijska skupina:** Ženama nepoznatog HIV statusa omogućeno je dobrovoljno („opt-in“) brzo HIV testiranje u klinici za porode. HIV pozitivnim ženama dan je Nevirapin. Primalje su strukturiranom procjenom utvrđivale jesu li HIV pozitivne žene uzele Nevirapin ponuđen u antenatalnim klinikama u toku trudnoće. One HIV pozitivne žene koje nisu uzele Nevirapin u antenatalnoj skrbi, dobile su ga u klinikama za porode. Djeca HIV pozitivnih majki primila su Nevirapin sirup prije otpusta iz bolnice. **Kontrolna skupina:** HIV pozitivne ženae testirane u antenatalnim klinikama na HIV primile su Nevirapin u slučaju da ga nisu bile dobile u antenatalnoj skrbi. Primalje su anketom utvrđivale jesu li HIV pozitivne žene uzele Nevirapin koji im je dan u antenatalnim klinikama. U kontrolnim se klinikama, žene nepoznatog HIV statusa ne mogu testirati na HIV. Djeca HIV pozitivnih majki su primila Nevirapin sirup neposredno prije otpusta iz bolnice.
Ishodi	Primarni ishod studije bio je obuhvaćenost majke i djeteta Nevirapinom. Obuhvaćenost majki Nevirapinom utvrđivala se ispitivanjem uzoraka krvi iz pupkovine. Pokrivenost djece Nevirapinom utvrđena je na temelju izvješća u njihovim zdravstvenim kartonima. Obuhvaćenost majki-djece Nevirapinom izmjerena je i u kontrolnim i intervencijskim klinikama tijekom dva razdoblja: prije i nakon provedbe intervencije.
Zabilješke	Postoje dva izvješća ovog istraživanja: doktorska disertacija, te članak

U intervencijskim klinikama, primalje su strukturiranom procjenom utvrđivale jesu li HIV pozitivne žene uzele Nevirapin ponuđen u antenatalnim klinikama u toku trudnoće. Strukturirana procjena uzimanja Nevirapina sastojala se od informacije o važnosti i svrsi Nevirapina te izjava koja opisuju pacijentov stav prema uzimanju Nevirapina. HIV pozitivne žene koje nisu uzele Nevirapin dan u antenatalnoj skrbi, dobile su ga u klinikama za porode. Ženama nepoznatog HIV statusa omogućeno je dobrovoljno („opt-in“) brzo HIV testiranje u klinici za porode, a HIV pozitivnim ženama dana je tableta Nevirapina (200 mg). Sve žene testirane na HIV infekciju bile su dužne potpisati pismeni pristanak u sklopu kojega su trebale odlučiti žele li znati rezultate testa prije ili nakon poroda. HIV negativnim žene dane su tablete kalcija kako bi se izbjeglo otkrivanje HIV statusa i potencijalna stigmatizacija.

U kontrolnim klinikama, HIV pozitivnim ženama, testiranim u antenatalnim klinikama na HIV, dan je Nevirapin u slučaju da ga nisu bile primile u antenatalnoj skrbi. Primalje su anketom utvrđivale jesu li HIV pozitivne žene uzele Nevirapin koji im je dan u antenatalnim klinikama. Žene nepoznatog HIV statusa, se u kontrolnim klinikama, nisu mogle testirati na HIV.

U svim (intervencijskim i kontrolnim) klinikama, djeca HIV pozitivnih majki morala su primiti Nevirapin sirup (2 mg/kg) prije otpusta iz bolnice.

Primarni ishod studije bio je pokrivenost majke i djeteta Nevirapinom. Pokrivenost majki Nevirapinom utvrđivala se ispitivanjem uzoraka krvi iz pupkovine. Uzorci krvi iz pupkovine prikupljeni su anonimno te su također korišteni za testiranje na HIV. U rijetkim slučajevima kada su rezultati analize krvi iz pupkovine te rezultati testiranja u antenatalnim klinikama bili nepodudarni, autori su rezultate analize krvi iz pupkovine držali točnim. Tekućinska kromatografija visoke djelotvornosti s pragom detekcije od 25 ng/ml Nevirapina korištena je za otkrivanje Nevirapina u uzorcima krvi iz pupkovine. Autori studije tvrde da je, pomoću ove metode, u njihovom prethodnom istraživanju, u krvi žena koje su prethodno, pred autorima, bile primile Nevirapin, on dokazan u više od 99% slučajeva.

Pokrivenost djece Nevirapinom utvrđena je na temelju izvješća u njihovim zdravstvenim kartonima. Pokrivenost majki-djece Nevirapinom izmjerena je i u kontrolnim i intervencijskim klinikama tijekom dva razdoblja: prije i nakon provedbe intervencije.

Isključene studije

Šest studija (35, 43-46) nije uključeno u ovaj sustavni pregled zbog neprikladne vrste studije (35, 43, 45, 46) te usmjerenosti na procjenu učinka poboljšanja kvalitete integriranih PMTCT programa, a ne učinka same integracije (44).

Nedovršene studije

Našli smo jednu relevantnu nedovršenu studiju (49) koja je trenutno u fazi odabira sudionika. Radi se o cluster randomiziranoj studiji koja se provodi u 12 klinika u Keniji. U intervencijskim klinikama, trudnicama će biti osigurana antenatalna skrb, PMTCT intervencije te HIV njega i liječenje na istom mjestu. U kontrolnim klinikama, trudnice će primati antenatalnu zaštitu te PMTCT intervencije na jednom mjestu dok će HIV njege i liječenja biti osigurani u odvojenoj klinici. Ishodi mjereni u ovoj studiji su stopa prijenosa HIV-a s majke na dijete, ishod liječenja HIV-a kod majki, zadovoljstvo zdravstvenog kadra poslom, udio djece testirane na HIV, udio bolesnica koje su započele te nastavile s HIV njegom i liječenjem. Studija će se razmotriti za uključenje u ovaj sustavni pregled čim rezultati postanu dostupni.

Rizik od sustavne pogreške u uključenoj studiji

Uključena cluster randomizirana studija imala je nizak rizik od sustavne pogreške pri odabiru sudionika, početne neravnoteže između skupina, gubitka cluster-a te pogrešne analize (Tablica 3). Iako su podaci za svih 12 cluster-a analizirani, 21% uzoraka krvi pupkovine nije ispitano zbog financijskih ograničenja. Ovi primjerci su podjednako podijeljeni između intervencijske i kontrolne skupine. Rezultati studije nisu usporedivi s rezultatima individualno randomizirane studije budući da studija nije a-priori imala dovoljnu snagu procjenjivati pojedine učinke intervencije zbog ograničenog broja klinika.

Tablica 3. Rizik od sustavne pogreške u uključenoj studiji

Sustavna pogreška	**Procjena rizika od sustavne pogreške**	**Informacije na kojima se temelji procjena**
Pogreške uvrštavanja sudionika	Nizak rizik	Citat iz studije: „Nakon završetka osnovnog nadzora, 12 klinika za porode stratificirano je prema veličini (na temelju broja poroda mjesečno) i njihovu dotadašnje pokrivenosti nevirapinom (na temelju podataka iz 2003. godine) te randomizirano u intervencijsku ili kontrolu skupinu."
Neujednačenosti obilježja sudionika u različitim cluster-ima	Nizak rizik	Citat iz studije: „ Jednadžbe generalizirane procjene (eng. *generalized estimating equations* ili GEE) korištene su za razvoj modela za utvrđivanje pokrivenosti nevirapinom u ovom istraživanju. GEE model je korišten zbog svoje sposobnosti da se prilagodi nedostatku neovisnosti pojedinaca ugniježđenih unutar klinike."
Gubljenjem cluster-a	Nizak rizik	Svih 12 cluster-a uključeno je u analizu.
Pogrešna analiza podataka	Nizak rizik	Citat iz studije: „ Jednadžbe generalizirane procjene (eng. *generalized estimating equations* ili GEE) korištene su za razvoj modela za utvrđivanje pokrivenosti nevirapinom u ovom istraživanju. GEE model je korišten zbog svoje sposobnosti da se prilagodi nedostatku neovisnosti pojedinaca ugniježđenih unutar klinike."
Usporedivosti s individualnom randomiziranom kontroliranom studijom	Mali rizik	Citat iz studije: „Naša studija nije imala a-priori snagu analizirati pojedinačne učinke brzog HIV testiranja ili strukturirane procjene uzimanja nevirapina.“

Učinak intervencije

Udio parova majka-dijete koji su primili Nevirapin smanjio se je u nadzornoj skupini s 53% na početku studije na 43%, nakon intervencije (raspon razlike u pokrivenosti Nevirapinom od -13% do 0%). U intervencijskim klinikama, udio parova majka-dijete koji su primili Nevirapin povećao se s 42% na početku studije, na 52% nakon intervencije (raspon razlike u pokrivenosti Nevirapinom od -10% do +33%). Relativan rizik pokrivenosti Nevirapinom

među parovima majki-dijete u intervencijskoj skupini, u usporedbi s nadzornom skupinom, je bio 0.89 na početku studije i 1.22 nakon intervencije. Ova razlika je rezultirala u omjeru relativnog rizika od 1.37 (RR 1.37, 95% CI, 1.04-1.77). Brzi HIV test u klinikama za porode povezan je s apsolutnim povećanjem u pokrivenosti Nevirapinom od 16% (raspon od 4 do 25%) u intervencijskim klinikama (od 0% na početku). U nadzornim klinikama nijedna žena nije testirana na HIV. Strukturirana procjena uzimanja Nevirapina bila je povezana s 4% povećanjem u pokrivenosti Nevirapinom u intervencijskim klinikama (od 63% na početku studije do 67% nakon intervencije), dok je u nadzornim klinikama uočen 9% pad (od 74% na početku do 65% nakon intervencije).

Kao dio ove cluster randomizirane studije, autori su proveli dodatno istraživanje u kojem su procjenjivali čimbenike koji utječu na pristajanje na HIV testiranje te uzimanje Nevirapina u klinikama za porode (50). Spomenuta je studija pokazala da je tek 29% žena nepoznatog HIV statusa testirana na HIV. Razlozi zbog kojih nisu bile testirane bili su neprikladnost za HIV testiranje, odbijanje testiranja, zauzetost zdravstvenog osoblja, prevelika bol ili uznapredovali porod. Prvorotke, te žene kojima u antenatalnim klinikama nije bilo ponuđeno testiranje, češće su pristajale na HIV testiranje. Od 13% HIV pozitivnih žena koje nisu dobile Nevirapin, većina ga je odbila primiti.

RASPRAVA

Sažetak glavnih rezultata

Ovaj sustavni pregled ukazuje na pomanjkanje dokaza temeljenih na pouzdanim, eksperimentalnim studijama o učinkovitosti integracije PMTCT programa s drugim zdravstvenim službama. Unatoč tom pomanjaknju dokaza, integracija PMTCT programa je ključna komponenta strategije SZO s ciljem povećanja udjela trudnica i njihove djece u PMTCT programima na 80%.

U jedinoj pronađenoj relevantnoj studiji, integracija PMTCT intervencija dovela je do povećanja udjela trudnica koje su primile Nevirapin od 10%, ali još uvijek nije ostvarila cilj SZO od 80%. Uvođenjem brzog HIV testa i strukturirane procjene uzimanja Nevirapina samo je 52% parova majka-dijete primilo Nevirapin.

Potpunost i primjenjivost dokaza

Izvršili smo sveobuhvatno pretraživanje brojnih baza podataka te uključili sve vrste studija koje Cochrane metodologija prihvaća, uključujući „interrupted time series“ studije te „controlled before and after“ studije. Ipak, pronašli smo samo jednu relevantnu studiju usmjerenu na utvrđivanje učinkovitosti integracije PMTCT intervencija s klinikom za porode.

Uključena cluster randomizirana studija imala je nizak rizik od sustavne pogreške. Ova studija ispituje učinak integracije dobrovoljnog, brzog HIV testiranja te strukturirane procjene uzimanja Nevirapina u klinikama za porode na udio HIV pozitivnih žena te njihove djece koji su primili Nevirapin. Istaknuti je da su PMTCT smjernice SZO značajno izmijenjene 2009. godine. Uključena je studija bila provedena u Zambiji tijekom 2005. i 2006. godine te na taj način prikazuje program koji je bio važeći prije izmjene smjernica. Studija nadalje ne pruža nikakve obavijesti o integraciji drugih PMTCT intervencija.

Na temelju ove jedne uključene studije nije moguće ponuditi nikakve preporuke o učinkovitosti te implementaciji integriranih PMTCT programa. Integracija PMTCT programa sa zdravstvenim ustanovama za porode je logična, budući da se dio PMTCT intervencija primjenjuje u toku te neposredno nakon poroda. No, i druge zdravstvene službe kao što su na primjer klinike za spolno prenosive bolesti ili za cijepljenje također bi mogle biti mjesto započinjanja PMTCT programa, što bi također trebalo istražiti.

Pretraživanjem literature pronašli smo brojne nekontrolirane, opservacijske studije o implementiranim integriranim PMTCT programima u zemljama u razvoju. Ovakav manjak visoko-kvalitetnih dokaza o učinkovitosti, isplativosti, načinu integracije različitih elemenata PMTCT programa te potencijalnih štetnih učinaka je zabrinjavajući. Financijska potpora za HIV/AIDS programe u zemljama u razvoju povećana je za 10 puta posljednjih 10ak godina. Iako SZO te druge međunarodne zdravstvene ustanove preporučuju integraciju PMTCT programa na temelju nekontroliranih opservacijskih studija te mišljenja stručnjaka, još uvijek postoji očigledna potreba za jačim dokazima koji bi usmjeravali ulaganje sredstava te poboljšali njihovu učinkovitost.

Potencijalne sustavne pogreške u sustavnom pregledu

Prednosti ovog sustavnog pregleda su jasni kriteriji uključivanja, detaljna pretraga bez metodoloških filtara, poštivanje Cochrane metodologije te stručnosti tima koji je proveo ovaj sustavni pregled, a sastojao se od metodološkog te tematskog stručnjaka. Cilj nam je bio na svaki način smanjiti opasnost od sustavne pogreške.

Rezultati drugih studija

Nedavno objavljen sustavni, pregledni članak u kojem se procjenjuje utjecaj PMTCT programa na zdravstvenu zaštitu trudnica i majki u zemljama u razvoju, pokazao je također mali broj studija te potrebu za daljnjim istraživanjem (51).

Studije koje smo isključili zbog neprikladnog dizajna pokazale su rezultate slične našem sustavnom pregledu. U isključenom "stepped wedge" istraživanju provedenom u Zambiji, integracija liječenja s ART-om u antenatalnim klinikama značajno je povećala udio žena koje su primile tu terapiju u usporedbi s djelomično integriranom skrbi gdje su žene bile upućivane iz antenatalnih klinika u posebne HIV centre da bi primile ART (46). S druge strane, retrospektivna, kohortna studija iz Južne Afrike procjenjivala je učinkovitost tri različita modela antenatalane zdravstvene skrbi te davanja ART-e: davanje ART-e ženama u antenatalnoj klinici, upućivanje žena iz antenatalne skrbi u posebnu, obližnju kliniku za ART te upućivanje žena iz antenatalne skrbi u kliniku za ART udaljenu do najviše 5 km. Nije pronađena nikakva značajna razlika u udjelu žena koje su primile ART između ova tri modela zdravstvene zaštite (35).

Obje studije pokazale su sveukupno malen udio žena koje su primile ART: 38% u "stepped wedge" istraživanju te 51% u kohortnoj studiji. U studiji uključenoj u ovaj sustavni pregled također je samo 16% žena nepoznatog HIV statusa bilo u klinikama za porode testirano na HIV, a samo je 46% parova majka-dijete primilo Nevirapin.

Druge dvije isključene studije imale su "before-and-after" strukturu (43, 45). U objema se studijama procjenjuje utjecaj integracije HIV testiranja i savjetovanja u antenatalnim klinikama na udio žena testiranih na HIV. Spomenute su studije pokazale značajan porast broja žena testiranih na HIV nakon integracije.

Zaključak

Integracija HIV testiranja i procjene primanja Nevirapina sa zdravstvenom zaštitom žena u klinikama za porode, značajno je povećala udio žena i djece koji su primili Nevirapin. Unatoč tom povećanju, ukupan je udio još uvijek nedovoljno visok. Nismo pronašli studije koje bi procjenjivale utjecaj integracije drugih perinatalnih PMTCT intervencija. Također ne postoje istraživanja s informacijama o isplativosti, utjecaju na zdravstvene radnike, stigmi ili kvaliteti integrirane zdravstvene skrbi. Pronašli smo brojne nekontrolirane, opservacijske studije koje su prikazivale postojeće integrirane PMTCT programe u zemljama u razvoju. Većina je spomenu-tih studija također pokazala značajno opadanje broja sudionica između pojedinih PMTCT intervencija. Iako ovakve studije pružaju važnu informaciju o ostvarivosti, propustima te preprekama provedbe, one ne mogu iznjedriti zaključak o učinkovitosti integriranja programa. Buduća bi istraživanja trebala, uz učinkovitost integrirane skrbi, analizirati isplativost, održivost, utjecaj na zdravstveni kadar, potencijalnu stigmu, te kvalitetu zdravstvene zaštite. Randomizirane studije možda nisu prikladne za ovo istraživanje, ali bi cluster randomizirane studije mogle dovesti do tih važnih saznanja. One pak studije koje bi uspjele odgovoriti na intrigantno pitanje učinkovitosti integracije PMTCT programa, trebale bi postati prioritetne.

SUMMARY

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 systematic review)

Background

Mother-to-child transmission of HIV (MTCT) 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.

Objectives

To assess the effect of integration of PMTCT measures with other healthcare services on uptake compared to stand-alone or partially integrated PMTCT interventions in low- and middle-income countries.

Methodology

Two authors independently ran the searches, selected studies, assessed methodological quality, and extracted data.

Main results

One cluster-randomised trial was included. It compared mother-infant Nevirapine coverage at labour ward between intervention clinics implementing rapid HIV testing and structured Nevirapine adherence assessment and control clinics implementing informal assessment of Nevirapine adherence. The study showed that the probability of Nevirapine coverage of mothers and infants in the intervention arm compared to control arm increased from 0.89 at baseline to 1.22 during the intervention period (RR 1.37, bootstrapped 95% CI, 1.041.77).

Conclusions

The included study showed significant improvement in coverage but only addressed the labour ward aspect of PMTCT programme. This weak evidence base does not allow any inferences regarding the effectiveness of integration of other PMTCT interventions, in other countries or contexts. Further research is urgently needed.

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KRATAK ŽIVOTOPIS

Rođena sam 05. listopada 1982. godine u Frankfurtu/Main u Saveznoj republici Njemačkoj. Osnovnu školu i opću gimnaziju „Marko Marulić“ završila sam u Splitu. Medicinski fakultet Sveučilišta u Splitu upisala sam 2001. godine, a završila 2007. godine. U toku studija primala sam stipendiju grada Splita zbog dobrog prosjeka ocjena. Po završetku dodiplomskog studija, započela sam pri Medicinskom fakultetu u Splitu poslijediplomski doktorski studij "Klinička medicina utemeljena na dokazima". Obavezni jednogodišnji, pripravnički staž odradila sam pri Ustanovi za Hitnu medicinsku pomoć u Splitu, a Državni stručni ispit položila pri Ministarstvu zdravstva Republike Hrvatske u listopadu 2008. godine. Sudjelovala sam u projektu *„Global burden of disease“* na London School of Hygiene and Tropical Medicine. Posljednje sam tri godine honorarni, znanstveni novak na „Katedri za obiteljsku medicinu i javno zdravstvo“ Sveučilišta Imperial u Londonu, Ujedinjeno Kraljevstvo. Stanovito sam vrijeme radila u ustanovi za Hitnu medicinsku pomoć u bolnici Charing Cross u Londonu. Pohađala sam nekoliko radionica Cochrane kolaboracije (Berlin, BRD 2010.) te sukladno tome sudjelovala u razvijanju ustroja Tečaja o sustavnim preglednim člancima za studente poslijediplomskih studija Sveučilišta Imperial u Londonu. Magisterij: *“Msc in Health Economics, Management and Policy”*započela sam na London School of Economics u Londonu u rujnu 2011. godine. Član sam Hrvatske liječničke komore, Hrvatskog liječničkog zbora, Hrvatskog liječničkog katoličkog društva, te Liječničke komore u Velikoj Britaniji („General Medical Council“). Autor sam i koautor više od 20 znanstvenih i stručnih radova. Sudjelovala sam aktivno i pasivno na više domaćih i međunarodnih znanstvenih i stručnih skupova.

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 (Review)

Tudor Car L, van-Velthoven MHMMT, Brusamento S, Elmoniry H, Car J, Majeed A, Atun R

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[Intervention Review]

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

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Editorial group: Cochrane HIV/AIDS Group.
Publication status and date: New, published in Issue 6, 2011.
Review content assessed as up-to-date: 24 April 2011.

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.

ABSTRACT

Background

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.

Objectives

To assess the effect of integration of perinatal PMTCT measures with other health care services on coverage and service uptake compared to stand-alone PMTCT programmes and healthcare services or partially integrated PMTCT interventions.

Search methods

We searched the following databases, for the time period of January 1990 to August 2010: MEDLINE, EMBASE, the WHO Global Health Library, CAB abstracts, CINAHL, POPLINE, PsycINFO, Sociological Abstracts, ERIC, AEGIS, Google Scholar, New York Academy of Medicine Grey Literature, Open SIGLE, British Library Catalogue, ProQuest Dissertation & Theses Database and U.S. National Library of Medicine Gateway system. We also searched t*he Cochrane Database of Systematic Reviews* (*the Cochrane Library* 2010, Issue 7), the Cochrane Central Register of Controlled Trials (*the Cochrane Library* 2010, Issue 7), Database of Abstracts of Reviews on Effects (*the Cochrane Library* 2010, Issue 7). We also searched for ongoing trials in the WHO International Clinical Trials Registry and Controlled clinical trials (January 1990 to July 2010). We performed ISI Web of Knowledge Cited Reference Search and scanned

the reference lists of the included articles for additional relevant studies. We contacted authors to locate additional eligible studies. To maximise sensitivity we did not employ any methodological filters.

Selection criteria

Randomised controlled trials (RCT), cluster-randomised controlled trials (cluster RCT), controlled clinical trials (CCT), controlled before and after (CBA) studies and interrupted time series (ITS) studies comparing integrated PMTCT interventions to non-integrated or partially integrated care for pregnant women, mothers and their infants in low- and middle-income countries.

Data collection and analysis

Two review authors independently ran the searches, selected studies, assessed methodological quality, and extracted data. The third review author resolved any disagreements.

Main results

Only one study met the inclusion criteria. A cluster-randomised trial (12 clusters, n=7664), compared mother-infant nevirapine coverage at labour ward between intervention clinics implementing rapid HIV testing with structured nevirapine assessment and control clinics implementing informal assessment of nevirapine adherence. The authors measured nevirapine coverage in all clinics at baseline and after the implementation of the intervention. An increase of 10% (range of difference in coverage from -10% to +33%) was observed in the intervention sites compared to 10% decline in mother-infant coverage in the control sites (range of difference in coverage from -13% to 0%). The study showed that the probability of nevirapine coverage of mothers and their infants in the intervention arm compared to control arm increased from 0.89 at baseline to 1.22 during the intervention period, representing a multiplicative effect of 1.37 upon the ratio of relative risks at baseline (RR 1.37, bootstrapped 95% CI, 1.041.77). The study had a low risk of bias. No studies were found that evaluated the effectiveness of integrating other perinatal PMTCT interventions with healthcare services.

Authors' conclusions

We found only one study suggesting that integrating perinatal PMTCT interventions with other healthcare services in low- and middle-income countries increases the proportion of pregnant women, mothers and infants receiving PMTCT intervention. The weak evidence base does not enable making any inferences for other countries or contexts. The study that met the inclusion criteria assessed only the impact of integrating PMTCT intervention in labour ward on the proportion of mothers and their infants receiving nevirapine. The study showed significant improvement in intervention coverage but it only addressed the labour ward aspect of PMTCT programme. We did not find sufficient evidence to make definitive conclusions about the effectiveness of integration of these interventions with other health services rather than providing them as stand-alone services. Further research is urgently needed to assess the effect of integrating perinatal prevention of mother-to-child HIV transmission interventions with other health services on intervention coverage, service uptake, quality of care and health outcomes and the optimal integration modality.

PLAIN LANGUAGE SUMMARY

Integrating interventions for prevention of transmission of HIV from mothers to infants during pregnancy, delivery and breastfeeding with other healthcare services to increase the coverage

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.

BACKGROUND

Women in reproductive years (i.e. aged 15 to 44 years) represent 50% of the HIV infected population in sub-Saharan Africa (UNAIDS 2010). Globally, HIV/AIDS is the leading cause of mortality among women of this age. Furthermore, each day an estimated 1,000 children under the age of 15 years acquire HIV infection. Over 90% of HIV infections in children under the age of 15 years are due to mother-to-child transmission and more than 90% of the mother-to-child transmission occurs in sub-Saharan Africa (UNAIDS 2010). Without preventive interventions in low- and middle-income countries, the risk of transmission of HIV from mother-to-child ranges between 15% and 40%; 5%-10% during pregnancy, 10%-20% during labour and delivery, and 5%-20% through breastfeeding (De Cock 2000).

In high-income countries, the MTCT rate has been decreased to around 1% through specific prevention of mother-to-child HIV transmission (PMTCT) interventions. The World Health Organization (WHO) categorises the interventions aimed at preventing mother-to-child transmission of HIV into four prongs: 1) primary prevention of HIV infection in women; 2) prevention of unintended pregnancy among HIV-positive women; 3) reducing transmission from HIV infected pregnant and lactating women to their children; and 4) care and support of women, infants, and families infected and affected by HIV/AIDS (WHO/UNFPA/IPPF 2005). The third prong of the PMTCT measures i.e. perinatal PMTCT programmes consist of provision of antiretroviral therapy (ART) or antiretroviral (ARV) prophylaxis to women during pregnancy and labour, and to infants postpartum, safe obstetric practices and infant feeding counselling. These interventions have proved to be both effective and cost-effective in reducing mother to infant HIV transmission (Paintsil 2009; Mofenson 1999; Scotland 2003; Sweat 2004). However, the evidence for effectiveness and cost-effectiveness of integrated PMTCT programmes is lacking.

At the United Nations General Assembly Special Session (UNGASS) in 2001, a goal was set to reduce the proportion of HIV infected infants by 50% by 2010. In order to achieve this target, 80% of pregnant women and their children need to receive essential prevention, treatment and care (UN 2001). Accordingly, global funding for HIV/AIDS programmes in low-income and middle-income countries has increased from 1.6 billion US$ in 2001 to 15.9 billion US$ in 2009 (UNAIDS 2010).

In spite of the goal set by the United Nations, significantly increased financing for HIV prevention and treatment in low- and middle-income countries, and the proven cost-effectiveness of PMTCT interventions, the coverage of women and children with PMTCT interventions remains unacceptably low (Johnson 2009; Gloyd 2007). In 2009, an estimated 26% of pregnant women in low- and middle-income countries were tested for HIV, and 53% [40%-79%] of the estimated HIV-infected pregnant women received at least some type of ART. Only 15% [10%-28%] of the estimated number of infants born to pregnant women living with HIV were reported to have received early infant HIV testing (WHO/UNAIDS/UNICEF 2010).Coverage was below 50% in 11 of the 25 countries with the largest number of women needing antiretroviral therapy to reduce mother-to-child transmission (WHO/UNAIDS/UNICEF 2010). Several publications and studies which discuss rapid and effective scale-up of PMTCT programmes in low-income countries (WHO/UNAIDS/UNICEF 2010; Ginsburg 2007; WHO 2005; WHO 2006), including a recent publication by the WHO (WHO 2010), recommend integration of PMTCT services with other health services or programmes targeting women and children as a key strategy to achieve equitable and universal access to health and improving health and survival of women and children in countries with a high burden of HIV. Integration is considered a key strategy to achieve equitable and universal access to health and to improve health and survival of women and children in countries with a high burden of HIV.

When PMTCT programmes were initially introduced in low- and middle-income countries, they were stand-alone programmes, with gradual integration into maternal and newborn healthcare services (Mazia 2009; Nkonki 2007). The rationale for integration of PMTCT interventions with maternal and newborn healthcare services is that these services temporally coincide with pregnancy, labour, delivery and early postpartum. Further, majority of women in low- and middle-income countries attend antenatal clinic at least once (in low-income countries 69% of pregnant women, in

lower-middle-income countries 79% of pregnant women and in upper-middle income countries 94% of pregnant women) (World health statistics 2010). This creates an opportunity for reaching women and children at high risk of or already infected with HIV (WHO 2006).

Attending the antenatal clinic once during pregnancy is, however, not enough to provide all steps of the PMTCT programme. The proportion of pregnant women having at least four antenatal clinic visits during pregnancy is much lower; 39% in low-income countries, 47% in lower-middle-income countries and 75% in upper-middle-income countries (World health statistics 2010). As for births attended by skilled health personnel, the proportion in low-income countries is 43%, in lower-middle-income countries 65% and in upper-middle-income countries 95% (World health statistics 2010). Therefore, pregnant women not attending maternal and child healthcare services will not be reached by PMTCT programmes integrated with these services. In addition, integrated or not, PMTCT services experience loss-to follow-up at each step of the programme delivery: from the first contact, through counselling, testing, collecting results, receiving antiretroviral therapy (ART), infant treatment, feeding recommendation, and postnatal follow-up (WHO/UNAIDS/UNICEF 2010; Msellati 2009). For example, based on data from multi-country PMTCT programme implemented by the Elizabeth Glaser Paediatric AIDS Foundation, of 100 pregnant women that might attend antenatal clinic, 92 are counselled, 77 are tested for HIV and 69 receive test results. Of eight women identified as HIV positive, six receive ARV prophylaxis. Of infants born to identified HIV positive women, only four will receive prophylaxis (Ginsburg 2007).

The importance of PMTCT measures and their integration with, for example, maternal and newborn healthcare services becomes even more evident when considering the 'feminisation' of the HIV/AIDS pandemic (i.e. increased vulnerability of women to HIV infection) (WHO 2006). Women are twice as likely to become HIV infected during unprotected heterosexual intercourse with an HIV-positive partner. The risk is further increased by gender inequality, power imbalance, poverty, lack of education and sexual violence (Quinn 2005). Collectively, these have fuelled the rise of HIV in women and paediatric HIV infections as a result of MTCT prompting the UN Secretary General and key UN Agencies to call for increased domestic and international financing to address health of women and children in general to reach the 4^{th} and 5^{th} Millennium Development Goal and to expand PMTCT coverage (UN Secretary General's Strategy 2010).

Our preliminary searches found a systematic review on integration of sexual and reproductive health services with HIV services produced by the WHO in 2009 (WHO 2009). This systematic review, framed around the 'four prongs' of PMTCT defined by the WHO, focused on integration of the first, the second and the fourth group of PMTCT strategies while the third group was excluded if the interventions were not linked to other areas of sexual and reproductive health (SRH). In addition, we found several related literature overviews which did not employ systematic review methods (Church 2009; Dehne 2000; Druce 2006; Moore 2003).

Definition of integrated care

There are many different definitions of integrated health care and the manner in which different healthcare services are integrated in developing countries varies (Atun 2010a; Shigayeva 2010; Mills 1983; Criel 1997). While there is no consensus on the definition of *integrated care*, two main concepts can be distinguished within the literature: a) an organizational structure focused on economic benefits, or b) a way of organizing service delivery (Strandberg-Larsen 2009).

Although integration is a process that occurs at different levels of the health system (regional, district, health facility) and in relation to key health system functions (i.e. governance, financing, planning, service delivery, monitoring and evaluation, demand generation) (Atun 2010b), integration at the health facility (i.e. the service delivery level) level is crucial for development of comprehensive set of services that can be accessed by users (WHO 2006). One of the main determinants of success and potential benefits of integration of PMTCT with other programmes is the increased access to and utilization of services (IPPF 2009;Inter-Agency 2007). This review primarily evaluates the effect of integration of PMTCT with other health services on the coverage and uptake (utilization) of PMTCT programmes and hence focuses only on integration of service delivery. We operationally define the integration of PMTCT programmes and other healthcare services as joining of service delivery of PMTCT programmes with other healthcare services either at a single point of access (unified) or by using referrals (WHO 2009). Integrated programmes using referrals for PMTCT interventions are defined as partially integrated.

How the intervention might work

Integration of PMTCT with related health services could improve the access to and uptake of PMTCT interventions in women and infants. Such integration could improve the quality of antenatal and maternity care, not only for the clients receiving PMTCT services but for all women and their children through more synergistic use of the available resources, training, monitoring and evaluation. Integration with maternal and newborn healthcare services could: catalyse the inclusion of PMTCT services with other healthcare services offered to pregnant women, women in labour, mothers and infants; help reduce the stigma experienced by HIV positive women (a key obstacle to the uptake of prevention, testing and treatment in women living with HIV); and reduce the duplication of services and competition for scarce resources. In low- and middle-income countries by using existing personnel along with additional funding and training, these integrated programmes could

be performed in existing facilities, thereby resulting in better utilisation of scarce human and financial resources for health (IPPF 2009; Israeli 2003).

However, integrating new healthcare services could overburden already weak health systems in resource-limited settings. For example, integration of early infant diagnosis within childhood immunization programmes increases the work load potentially leading to poorer service delivery and failure to administer timely HIV testing (Cherutich 2008). Lack of resources, leadership and monitoring could negatively impact on the implementation and sustainability of the integrated services. PMTCT programme training could lead to a brain drain of ante- or perinatal care workers and PMTCT programme trained workers to other better-funded AIDS programmes and thereby further reduce already scarce human resources. If integrated care is organised so as to provide separate consultation rooms for HIV positive women, this could jeopardize privacy of HIV positive clients and further increase the stigma experienced by these women and deter other women from using services integrated with PMTCT, such as antenatal clinic or child health services. The personnel could express unease about providing care to HIV infected or potentially infected clients (although they would have done that unknowingly) leading to discrimination, negative attitudes and inadequate quality of care from providers (Druce 2006; Rutenberg 2004). Provision of ART services within antenatal care and referral of HIV positive women to HIV clinics after the delivery could lead to high attrition rates (Stinson 2010). Furthermore, HIV positive women opting for breastfeeding require continuation of ART or provision of ART to their infants for up to one year. Given the weak infrastructure and health systems, it is questionable if integrating these interventions within maternity services is feasible.

Why it is important to do this review

The timeliness of this review is apparent given the recent international commitment to scale-up PMTCT programmes in low- and middle-income countries. The UN Secretary General, G8 countries, and the Global Fund to Fight AIDS, Tuberculosis and Malaria, in collaboration with its key partners the Joint United Nations Programme on HIV/AIDS (UNAIDS), the WHO, the United Nations Children's Fund (UNICEF), the United Nations Population Fund (UNFPA) and the Children's Investment Fund Foundation (CIFF) have committed to further develop and improve the quality and effectiveness of PMTCT services in low- and middle-income countries (G8 Muskoka Declaration 2010; UN Secretary General's Strategy 2010). Integration of PMTCT and other related services is a crucial component of their strategy (Global Fund 2010). To date, there has been no systematic analysis of the effects of integration of PMTCT programmes with other healthcare services in low- and middle-income countries on the uptake of PMTCT interventions. Given the importance of the question and unsatisfactory evidence base, there is an urgent need to systematically evaluate effectiveness of integrated PMTCT programmes. This systematic review will inform current and new initiatives aimed at increasing PMTCT coverage, and help focus funding on the best modalities for delivering PMTCT interventions.

OBJECTIVES

To assess the effect of integration of perinatal PMTCT interventions with other health care services on the proportion of pregnant women, mothers and infants receiving PMTCT interventions compared to stand alone PMTCT programmes and health care services or partially integrated PMTCT interventions with other health programmes. Other health care services include maternal, newborn, and child health services; general HIV care; treatment and support services for sexually transmitted infection; HIV counselling and testing services; sexual and reproductive health services.

METHODS

Criteria for considering studies for this review

Types of studies

Given the anticipated small number of randomised controlled trials (RCTs) which may not provide conclusive answers, we also included cluster-randomised controlled trials (cluster RCT), controlled clinical trials (CCT), controlled before and after (CBA) studies, and interrupted time series (ITS) studies. We considered eligible CBA studies that have contemporaneous data collection before and after the intervention and an appropriate control site or activity. As for ITS studies, they had to have a clearly defined time when the intervention had occurred and at least three data points before and three after the intervention to be considered eligible.

Types of participants

We included studies focusing on pregnant women and infants with unknown HIV serostatus (integration of maternal or infant HIV testing with other services) and HIV-positive pregnant women and lactating mothers (integration of interventions, such as ART or ARV prophylaxis provision, Caesarean delivery and infant feeding counselling with other health services) in developing countries. Developing countries were defined as the World Bank categories of low-income, lower-middle-income or upper-middle-income economies (World Bank 2010).

Types of interventions

According to the WHO, PMTCT programmes include four prongs (see above) (WHO/UNFPA/IPPF 2005). We focused our review on the third prong of measures - *perinatal PMTCT interventions*. This package of specific, high-impact PMTCT interventions, essential for maximally effective reduction of MTCT includes: 1) identifying HIV status in pregnant women; 2) reducing maternal viral load with ART; 3) provision of ARV prophylaxis to mother; 4) preventing exposure to HIV at birth through improved obstetric practice; 5) reducing exposure to HIV through breastfeeding by infant feeding counselling; 6) provision of ARV prophylaxis to the infant and 7) early infant diagnosis. We considered eligible studies focusing on integration of any (including more than one) of the perinatal PMTCT interventions with other health services. These include:

1) Antenatal clinic
2) Delivery/obstetric/labour ward care
3) Postnatal care
4) Neonatal/newborn care
5) Paediatric/infant care
6) Nutritional programmes
7) HIV testing and support centres
8) HIV treatment centres
9) Reproductive/gynaecological services
10) Sexually transmitted infection clinics
11) Family planning
12) Primary health care
13) Emergency care
14) Tuberculosis clinics
15) Malaria clinics
16) Immunization
17) Any other service

The comparison intervention for the review was usual care/practice, including non-integrated health services (stand-alone PMTCT services) or PMTCT programmes partially integrated with any other health service. Partially integrated PMTCT programmes were defined as programmes where women attending healthcare services were referred to a separate facility to receive PMTCT interventions.

Types of outcome measures

Primary outcomes

Effectiveness of PMTCT programme measures

- Percentage of pregnant women living with HIV who received ARV prophylaxis or ART
- Percentage of pregnant women provided with information on PMTCT
- Percentage of pregnant women tested for HIV, including those previously confirmed to be living with HIV
- Percentage of pregnant women living with HIV having a safe delivery either at home or hospital
- Percentage of pregnant women living with HIV who received infant feeding counselling
- Percentage of infants born to women living with HIV receiving antiretroviral prophylaxis
- Percentage of infants born to women living with HIV who received HIV test

Secondary outcomes

- Percentage of HIV-negative infants born to women living with HIV
- Cost-effectiveness of integrated service delivery
- Impact on human resources
- Overall quality of care
- Impact on stigma

Search methods for identification of studies

We used a comprehensive search strategy to identify all relevant research in any language but with an English abstract and regardless of publication status. We limited our searches to periods after 1990 because this was the year of implementation of the first PMTCT programmes (CHG 2004). We used a highly sensitive search strategy developed by the Cochrane HIV/AIDS Review Group and combine that with the following terms:
(Mother-to-child transmission) OR MTCT OR (prevention of mother-to-child transmission) OR PMTCT OR (disease transmission, vertical) OR (perinatal transmission) OR (postnatal transmission) OR (maternal-infant transmission) OR (mother-to-infant transmission)
There is no internationally agreed definition of integrated care. Some authors, although focusing on integrated service delivery in their studies, could have potentially omitted this term or labelled the concept differently. Therefore, our search strategy did not entail search terms related to integrated care. We did, however, examine service delivery described in each study to decide if it fits our definition of healthcare service integration.
In our review we considered eligible the studies on integration of PMTCT programmes with any other health service. This represents an array of different programmes that also could have a wide range of labels. In an attempt to include terms for this wide range of health services in a search strategy, we believe we would have decreased its sensitivity.

Electronic searches

We searched MEDLINE (January 1990 to July 2010), EMBASE (January 1990 to July 2010), *the Cochrane Database of Systematic Reviews* (*the Cochrane Library* 2010, Issue 7), the Cochrane Central Register of Controlled Trials (*the Cochrane Library* 2010, Is-

sue 7), Database of Abstracts of Reviews on Effects (*the Cochrane Library* 2010, Issue 7), The WHO Global Health Library (January 1990 to August 2010), CAB abstracts (January 1990 to August 2010), CINAHL (January 1990 to August 2010), POPLINE (January 1990 to August 2010), PsycINFO (January 1990 to August 2010), Sociological Abstracts (January 1990 to August 2010), ERIC (January 1990 to August 2010), and U.S. National Library of Medicine Gateway system (January 1990 to August 2010).

Searching other resources

We also searched reference lists of relevant studies and performed ISI Web of Knowledge Cited Reference Search. We did not include potentially relevant conference proceedings or abstracts when we were not provided additional information.

We searched the WHO International Clinical Trials Registry (January 1990 to July 2010) and Controlled clinical trials (January 1990 to July 2010) for relevant on-going trials.

We attempted to find unpublished studies by searching grey literature sources, such AEGIS (January 1990 to August 2010), Google Scholar (January 1990 to August 2010), New York Academy of Medicine Grey Literature (January 1990 to August 2010), Open SIGLE (January 1990 to August 2010), British Library Catalogue (January 1990 to August 2010) and ProQuest Dissertation & Theses Database (January 1990 to August 2010). The Google Scholar search resulted in a large number of hits of which we scanned the first 500 results.

Data collection and analysis

Selection of studies

We exported and scanned search results using reference management software EndNote X4. Two authors independently reviewed the titles, abstracts and full-texts of potentially relevant studies for eligibility. The disagreements between authors were resolved by discussion and consensus. If the differences of opinion regarding study eligibility persisted, we involved a third reviewer to reach a decision. We drew an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart to present the study selection process (Moher 2010).

Data extraction and management

The data were extracted using a standardized data extraction form which summarised key information from the relevant studies, such as administrative data (title, author, publication status, year of publication, country and location of the study etc.); methods (stated study design, data relevant for risk of bias assessment, duration and completeness of follow-up); information on participants; interventions examined; outcomes assessed; comparison performed; and other notes. The data extraction was performed independently by two review authors. The disagreements were resolved by discussion and consensus between review authors. The third review author supported the other authors and resolved potential differences of opinion.

Assessment of risk of bias in included studies

Two review authors independently performed initial assessment of methodology and the quality of evidence and data extraction. Any disagreements were resolved by discussion. We planned to assess the included studies in accordance with the "risk of bias" tool described in the Cochrane Handbook for Systematic Reviews of Interventions and additional criteria developed by the Cochrane Effective Practice and Organisation of Care Group (EPOC) Group (Higgins 2008; EPOC 2002). Each criterion had to be rated as either yes (low risk of bias), unclear (uncertain risk of bias), or no (high risk of bias) (see Risk of bias in included studies).We did not find any eligible RCTs, CCTs, CBAs or ITSs.

We assessed the included cluster-randomised trial (cluster RCT) for the presence of recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability with individually randomised trials (Higgins 2008).

Dealing with missing data

We presented attrition rates for the outcomes of the included studies. We did not perform any imputation for missing outcome data.

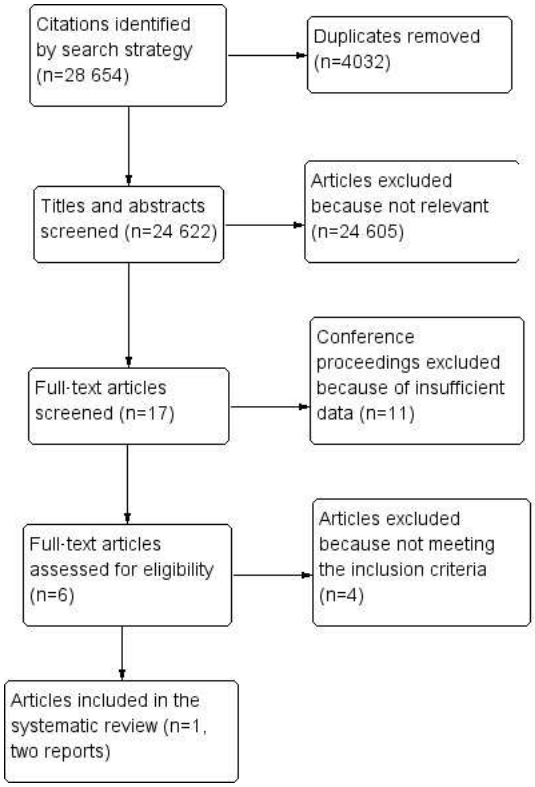
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The literature searches yielded 28,654 potentially relevant references. Screening of titles and abstracts resulted in six (Chege 2005; Kasenga 2008; Killam 2010; Megazzini 2010; Megazzini 2008; Stinson 2010; Van't Hoog 2005) records of which we included one study with two reports (Megazzini 2010; Megazzini 2008). In addition, we identified one potentially relevant ongoing trial (NCT00931216). We found 11 potentially relevant conference proceedings. We could not retrieve additional information, although we contacted authors. An adapted PRISMA flow-diagram of study selection can be found in (Figure 1).

Figure 1. Study flow diagram.



Included studies

We found only one eligible study, a cluster RCT with two reports in the form of a journal article and a thesis (Megazzini 2010; Megazzini 2008) (see Characteristics of included studies). This study was published in English language. It was conducted in Lusaka, Zambia in 12 public-sector delivery centres from October 2005 to January 2006. It included 7,664 women delivering at participating clinics. Six clinics were randomly assigned to the intervention arm and six to the control group. The services in all clinics were implemented by midwifes.

At the intervention sites, HIV positive women identified in antenatal clinics were administered a structured assessment of the adherence to nevirapine provided to them in an antenatal clinic. The nevirapine assessment consisted of information about the importance and purpose of nevirapine and statements describing the patient's attitude to nevirapine ingestion. In cases when HIV positive women had not taken the nevirapine provided in antenatal care, they were given nevirapine in labour ward. Women of unknown HIV status received opt-in rapid HIV testing at labour ward and nevirapine tablet (200 mg) if confirmed as HIV positive and were required to sign a written consent and indicate if they wanted to learn their result before or after the delivery. HIV negative women were offered a calcium tablet to avoid disclosure of HIV status and potential stigmatisation.

At the control clinics, HIV positive women identified in antenatal clinic were provided with nevirapine if not adherent to the ARV prophylaxis provided in antenatal care. To establish their adherence, midwifes would informally ask them if they have taken nevirapine. The control sites did not provide HIV testing of women of unknown HIV status.

All infants born to HIV positive mothers had to be provided with nevirapine syrup (2 mg/kg) in both the control and interventional clinics before the hospital discharge.

The primary outcome of the study was mother-infant coverage. Mothers' coverage was determined by the nevirapine testing of the umbilical cord blood specimens. Umbilical cord blood specimens were collected anonymously and were also used for HIV testing. In rare cases when the cord blood specimens analysis and antenatal clinic testing results were discordant, the authors considered the cord blood results to be correct. High performance liquid chromatography (HPLC) with a detection threshold of 25 ng/ml of nevirapine was used to detect nevirapine in cord blood specimens. Authors reported that in their previous study, nevirapine was detected using this method in >99% of women in whom nevirapine

ingestion had been observed directly.
Infants' coverage was determined based on the report of nevirapine administration in the patients' files. Mother-infant nevirapine coverage was measured in both control and interventional clinics during two periods: before and after implementation of the intervention.

Excluded studies

Six studies (Chege 2005; Kasenga 2008; Killam 2010; Stinson 2010; Van't Hoog 2005) were excluded; details can be found in Characteristics of excluded studies. The reasons for exclusion were: study not having an eligible study design (Kasenga 2008; Killam 2010; Stinson 2010; Van't Hoog 2005) and study assessing the effect of quality improvement of integrated PMTCT programmes rather than the effect of integration itself (Chege 2005).

Ongoing study

We found one relevant ongoing trial (NCT00931216) currently recruiting participants, a cluster RCT conducted at 12 clinics in Kenya. At intervention sites, pregnant women will be provided with antenatal clinic, PMTCT interventions and HIV care and treatment at the same clinic from the antenatal clinic provider. At the control sites, women attending antenatal clinic integrating PMTCT programme are referred to HIV care and treatment clinic located at the same facility. The outcomes measured in this trial are MTCT rates, maternal HIV treatment outcomes, provider job satisfaction, infant HIV testing uptake, patient enrolment, retention and adherence in HIV care and treatment. Data will be considered for inclusion in this review when available.

Risk of bias in included studies

The included cluster RCT had a low risk of recruitment bias, baseline imbalance, loss of clusters and incorrect analysis. Although data for all twelve clusters was analysed, 21% of the umbilical cord blood specimens were not tested because of financial constraints. These specimens were equally divided between the intervention and control arm. We assessed that the results of the study were not comparable with individually randomised RCT since authors reported that the study was not powered a priori to look at the individual effects of the intervention due to the limited number of labour wards.

Effects of interventions

The percentage of mother-infant pairs receiving nevirapine at the control sites declined from 53% in the baseline period to 43% in the intervention surveillance period (range of difference in coverage from -13% to 0%). At the intervention clinics, the percentage of mother-infant pairs receiving nevirapine increased from 42% in the baseline period to 52% during the intervention (range of difference in coverage from -10% to +33%). The relative risk of nevirapine coverage among mother-infant pairs in the intervention arm as compared with mother-infant pairs in the control arm was 0.89 at baseline and 1.22 during the intervention period. This change resulted in a ratio of relative risks of 1.37 (RR 1.37, bootstrapped 95% CI, 1.04-1.77). Rapid HIV testing at labour ward was associated with an absolute increase in coverage of 16% (range 4 to 25%) in the treatment clinics (from 0% at baseline, data not shown). Coverage among women in the control clinics was zero. The structured assessment of nevirapine adherence was associated with a 4% increase in coverage in the treatment clinics (from 63% at baseline to 67% during the intervention) compared with a 9% drop in coverage in the control clinics (from 74% at baseline to 65% during the intervention period).
As part of the included cluster RCT, authors performed a separate study assessing participants' predictors of testing acceptance and nevirapine administration in labour (Megazzini 2009). This study reported that only 29% of women of unknown HIV status and eligible for HIV testing at the labour ward were tested for HIV. The reasons for not being tested were not being identified as eligible, patient's refusal, counsellor not available or midwife too busy, mother in too much pain or in advanced labour. Women pregnant for the first time [adjusted odds ratio (AOR) 1.5; 95% confidence interval (CI): 1.1 to 2.1] and those who were not offered testing in antenatal clinic (AOR 3.7; 95% CI: 2.8 to 5.1) had greater odds of HIV testing acceptance. 13% of women did not receive nevirapine tablet in labour ward largely because they refused it.

DISCUSSION

Summary of main results

Our review shows there is almost no evidence from reliable, experimental design studies on the effect of integrating PMTCT interventions with other health services on intervention coverage, service uptake, quality of care and health outcomes. Despite this being a crucial component of an international WHO-led strategy to increase PMTCT coverage to 80% of pregnant women and their children.
The one high-quality study that met the inclusion criteria, while successful in achieving a 10% increase in nevirapine coverage fell over 30% short of the 80% target. Following a rapid HIV test and structured nevirapine assessment only 52% of mother-infant pairs received both a maternal and an infant dose of nevirapine.

Overall completeness and applicability of evidence

We performed a comprehensive search of a wide range of databases and considered eligible all Cochrane accepted experimental study designs including interrupted time series and controlled before and after studies. It is very unlikely that we missed any trial data.Yet we found only one eligible study addressing labour ward aspects of the PMTCT programme.

The included cluster RCT had a low risk of bias. This study presented the effect of integration of opt-in rapid HIV testing and implementation of structured nevirapine adherence assessment at labour ward on proportion of HIV positive women receiving nevirapine. The WHO guidelines on PMTCT have been substantially revised in 2009. The included study was conducted in 2005 and 2006 in Zambia, a low-income country and refers to the situation prior to the new guidelines. The study does not provide any insight into other steps of the PMTCT. For the true success in reduction of MTCT rates all steps are equally critical from HIV testing to infant feeding advice post-delivery.

We cannot make any recommendation about the implementation of integrated PMTCT programmes based on this one study. PMTCT programme integration with maternity services is logical given the coinciding timing of service delivery. However, other healthcare services, e.g. STI or immunization clinics can also be an important entry point to PMTCT programme and this should also be evaluated.

The performed searches resulted in a large number of uncontrolled observational studies reporting on integrated care programmes already implemented in developing countries. These will be included in a parallel review that will analyse a wider range of study designs.

Such lack of high quality evidence on effectiveness, cost-effectiveness, modality of integration of different elements of the PMTCT and potential adverse outcomes of integrated care is of great concern. Global funding for HIV/AIDS programmes in low-income and middle-income countries has seen an unprecedented tenfold increase in the last ten years. This should be guided by high-quality reliable evidence. Whilst integration has been recommended by the WHO and other international funding agencies based on expert opinions and uncontrolled observational studies this should not stop us from developing a stronger foundation for multibillion investments that could if nothing else help to optimise the guidance to maximise the impact of these large investments.

Potential biases in the review process

Strengths of this systematic review are many including explicit eligibility criteria, the comprehensive search without methodological filters, rigorous following of the Cochrane methodology and the review team including methodological and subject experts. We took every step to minimise potential biases in the review process.

Agreements and disagreements with other studies or reviews

A recently published systematic review evaluating the impact PMTCT programmes on maternal health care in resource-poor settings also reported low number of studies and a need for further research (Both 2010).

Our findings are consistent with the studies excluded because of an inadequate study design. In the excluded stepped wedged design study conducted in Zambia integration of ART provision within antenatal clinic significantly increased the proportion of eligible women receiving ART compared to partially integrated care where women were referred from antenatal clinic for ART to a separate HIV clinic (Killam 2010). On the other hand, a retrospective cohort study from South Africa evaluated three service models for provision of ART to eligible women attending antenatal clinic: provision of ART in the antenatal care, referral to the separate, stand-alone ART service on the same premises and referral to off-site ART services within a 5-km radius from antenatal care. The authors did not find any significant differences in the HAART coverage between these three service delivery models (Stinson 2010). However, both of these two studies evaluating integration of ART provision reported an overall low proportion of eligible women receiving ART: 38% in the stepped wedge design and 51% in the cohort study. These missed opportunities in the uptake of PMTCT services have also been observed in the included cluster RCT where labour ward based HIV testing was performed in only 16% of women with unknown HIV serostatus and only 46% of mother-infant pairs received both a maternal and infant doses of nevirapine.

The other two excluded studies employed before and after study design (Kasenga 2008; Van't Hoog 2005). Both studies evaluated the effect of integration of HIV testing and counselling within antenatal care on HIV testing uptake and showed a significant increase in proportion of women tested.

AUTHORS' CONCLUSIONS

Implications for practice

Integrating HIV testing and nevirapine adherence assessment at labour ward resulted in substantial increase in mother-infant nevirapine coverage. While the increase was statistically significant, it is far from satisfactory from the point of minimising the chances of transmission of HIV. We did not find any research assessing the impact of integrating other perinatal PMTCT interventions on coverage. There is also no published information on cost-effectiveness, impact on human resources and stigma and quality of care. We found a number of programme evaluations indicating a wide spread implementation of integrated PMTCT programmes in developing countries. Most of these studies, like ours, reported

a marked loss to follow-up between each of the steps of PMTCT programmes.

Implications for research

The searches identified a number of observational studies evaluating integrated PMTCT programmes in developing countries. These studies could provide valuable information about the feasibility, gaps and barriers to implementation. However, they do not provide robust evidence on which we could conclude that integrated care is more effective than non-integrated or partially integrated or about the modality of integration. Although assessing the effectiveness of integrated care is crucial, other outcomes such as cost-effectiveness, sustainability, impact on human resources, stigma and quality of care are of equal importance. RCT study design may not be suitable for evaluating these outcomes, but high quality cluster RCTs, CBAs and ITSs could provide the much needed answers. Policy makers should ensure urgent prioritisation of rigorous research on integration of PMTCT.

ACKNOWLEDGEMENTS

We are very grateful to Tapio Paljarvi who ran the searches, removed the duplicate citations and contributed to the study selection process. We would like to express our gratitude to Joy Oliver from the Cochrane HIV/AIDS group and Rosemary J. Brownhill and Emma L. Shaw from Medicine Central Library, Imperial College London for helping us develop the search strategy. We are also very grateful to Tara Horvath and the rest of the Cochrane HIV/AIDS group for their support and guidance.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Megazzini 2008

Methods	Cluster RCT conducted in Lusaka Zambia at 12 public-sector delivery centres from October 2005 to January 2006. Six clinics were randomly assigned to the intervention arm and six to the control group. The services in all clinics were implemented by midwifes
Participants	7664 women delivering at participating clinics
Interventions	Intervention sites: Women presenting at labour ward with unknown HIV serostatus were provided with opt-in rapid HIV testing, and if resulting HIV positive received nevirapine. HIV positive women coming to labour ward were administered a structured nevirapine adherence assessment, and if indicated, subsequently received nevirapine. Infants born to HIV positive women had to receive nevirapine syrup before discharge from the hospital Control sites: HIV positive women presenting at the labour ward were informally asked if they had taken the nevirapine given to them in the antenatal care. If not adhering to the provided nevirapine, they were offered the prophylaxis at the labour ward. Infants born to HIV positive women had to receive nevirapine syrup before discharge from the hospital
Outcomes	The primary outcome of the study was mother-infant coverage. Mother's coverage was determined by measuring nevirapine in the umbilical cord blood specimens. The infant's coverage was determined based on the report of nevirapine administration in the patient file
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Free of recruitment bias	Low risk	"Following completion of the baseline surveillance, the 12 labor wards were stratified according to size (based on the number of deliveries per month) and their historical nevirapine coverage level (based on the 2003 surveillance data) and randomised to the treatment or control arms."
Free of baseline imbalance	Low risk	"Generalized estimating equations (GEE) were used to develop a model determining NVP coverage in this study. A GEE model was used because of its ability to adjust fir the non-independance of individuals nested within a clinic."

Megazzini 2008 (*Continued*)

Free of loss of clusters	Low risk	All 12 clusters were included in the analysis
Free of incorrect analysis	Low risk	"Generalized estimating equations (GEE) were used to develop a model determining NVP coverage in this study. A GEE model was used because of its ability to adjust fir the non-independance of individuals nested within a clinic."
Comparability with individually randomised trials	High risk	"Our study was not powered a priori to look at the individual effects of rapid HIV testing or the rapid assessment of NVP adherence."

Megazzini 2010

Methods	Cluster RCT conducted in Lusaka Zambia at 12 public-sector delivery centres from October 2005 to January 2006. Six clinics were randomly assigned to the intervention arm and six to the control group. The services in all clinics were implemented by midwifes
Participants	7664 women delivering at participating clinics
Interventions	Intervention sites: Women presenting at labour ward with unknown HIV serostatus were provided with opt-in rapid HIV testing, and if resulting HIV positive received nevirapine. HIV positive women coming to labour ward were administered a structured nevirapine adherence assessment, and if indicated, subsequently received nevirapine. Infants born to HIV positive women had to receive nevirapine syrup before discharge from the hospital Control sites: HIV positive women presenting at the labour ward were informally asked if they had taken the nevirapine given to them in the antenatal care. If not adhering to the provided nevirapine, they were offered the prophylaxis at the labour ward. Infants born to HIV positive women had to receive nevirapine syrup before discharge from the hospital
Outcomes	The primary outcome of the study was mother-infant coverage. Mother's coverage was determined by measuring nevirapine in the umbilical cord blood specimens. The infant's coverage was determined based on the report of nevirapine administration in the patient file
Notes	Secondary report

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Free of recruitment bias	Low risk	"Following completion of the baseline surveillance, the 12 labor wards were stratified according to size (based on the number

		of deliveries per month) and their historical nevirapine coverage level (based on the 2003 surveillance data) and randomised to the treatment or control arms. The use of stratification was intended to create balance between arms"
Free of baseline imbalance	Low risk	"We used generalized estimating equations (GEE) to determine the odds of coverage associated with the intervention, adjusting for the nonindependence of individuals within clinics. Given the known tendency of GEE to underestimate standard errors when the number of clusters is small, we used permutation tests to validate any significant results from the GEE models. Due to the prospective nature of the study, the parameters for the estimated GEE model were used to estimate probability of coverage.To estimate relative risk, the ratio of the probability of coverage in treatment clinics to the probability of coverage in control clinics was calculated. Variables significant in the bivariate GEE model at P<0.10 were included in the multivariable model. To provide 95% confidence intervals for point estimates produced by the GEE models, 1000 bootstrap samples were drawn based upon the stratified randomisation design of the study. The 2.5th and 97.5th bootstrap percentiles defined our reported 95% confidence intervals."
Free of loss of clusters	Low risk	All 12 clusters were included in the analysis
Free of incorrect analysis	Low risk	"We used generalized estimating equations (GEE) to determine the odds of coverage associated with the intervention, adjusting for the nonindependence of individuals within clinics. Given the known tendency of GEE to underestimate standard errors when the number of clusters is small, we used permutation tests to validate any significant results from the GEE models. Due to the prospective nature of the study, the parameters for the estimated GEE model were used to estimate probability of coverage.To estimate relative risk, the ratio of the probability of coverage in treatment clin-

		ics to the probability of coverage in control clinics was calculated. Variables significant in the bivariate GEE model at P<0.10 were included in the multivariable model. To provide 95% confidence intervals for point estimates produced by the GEE models, 1000 bootstrap samples were drawn based upon the stratified randomisation design of the study. The 2.5th and 97.5th bootstrap percentiles defined our reported 95% confidence intervals."
Comparability with individually randomised trials	High risk	"Owing to the limited number of labor wards available for participation, this study was not powered a priori to look at the individual effects of rapid HIV testing or the rapid nevirapine adherence assessment."

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chege 2005	This was a CBA study assessing the effect of quality improvement intervention (i.e. in-service training of staff and the supply of essential equipment) on uptake of comprehensive antenatal care which included also PMTCT services
Kasenga 2008	The study was a repeated cross sectional study providing data on PMTCT intervention uptake before and after the integration of PMTCT services within antenatal care
Killam 2010	The study was an non-randomised stepped wedge trial evaluating the effect of integration of ART provision within antenatal care compared to referral of antenatal care attendees to ART clinic on ART coverage
Stinson 2010	The study was a retrospective cohort study evaluating the effect of integration of ART provision within antenatal care compared to referral of antenatal care attendees to nearby and off-site ART clinic on ART coverage
Van't Hoog 2005	The study was a before and after study evaluating PMTCT intervention uptake before and after the integration of PMTCT services within antenatal care

Characteristics of ongoing studies *[ordered by study ID]*

NCT00931216

Trial name or title	Integration of HIV Care and Treatment Into Antenatal Care in Migori District, Kenya
Methods	This study is cluster RCT. Twelve antenatal care clinics in Migori district, Kenya have been randomly assigned to either integrated or control arm
Participants	All HIV positive pregnant women attending antenatal care clinics included in the study
Interventions	At the intervention clinics, pregnant women will be provided with antenatal care, PMTCT interventions and HIV care and treatment (including ART if required) at the same clinic. At the control clinics, women will receive antenatal care and PMTCT services with referral to the HIV care and treatment department located in the same facility
Outcomes	The outcomes measured in this trial are the MTCT rates, maternal HIV treatment outcomes, provider job satisfaction, infant HIV testing uptake, patient enrolment, retention and adherence in HIV care and treatment
Starting date	June 2009
Contact information	Craig R Cohen, MD, MPH University of California, San Francisco
Notes	This study is currently recruiting participants. Its estimated primary completion date is May 2011

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. AEGIS search strategy

(mother-to-child OR MTCT OR mother-to-child OR PMTCT OR postnatal transmission OR prenatal transmission OR vertical transmission OR HIV transmission OR mother-to-infant OR maternal-to-child OR maternal-infant)

Appendix 2. British Library Catalogue (BETA) search strategy

(mother-to-child OR MTCT OR mother-to-infant OR adult-to-child OR maternal-to-child OR vertical transmission OR perinatal transmission OR postnatal transmission OR post natal transmission OR maternal-infant transmission OR PMTCT) AND (HIV OR AIDS)

Appendix 3. CAB abstracts search strategy

Topic = (mother-to-child OR MTCT OR mother-to-infant OR adult-to-child OR maternal-to-child OR vertical transmission OR perinatal transmission OR postnatal transmission OR post natal transmission OR maternal-infant
AND
Topic = (HIV OR hiv-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV infect* OR human immunodeficiency virus OR human immunedeficiency virus OR human immune-deficiency virus OR human immuno-deficiency virus OR human immun* deficiency virus OR acquired immunodeficiency syndrome OR acquired immunedeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR acquired immun* deficiency syndrome transmission OR PMTCT)

Appendix 4. CINAHL search strategy

("mother-to-child" OR MTCT OR "mother-to-child" OR "mother-to-infant" OR "adult-to-child" OR "maternal-to-child" OR "vertical transmission" OR "perinatal transmission" OR "prenatal transmission" OR "postnatal transmission" OR "post natal transmission" OR "maternal-infant transmission" OR PMTCT) and (HIV OR HIV-1* OR HIV-2* OR HIV-1 OR HIV2 OR "HIV infect*" OR "human immunodeficiency virus" OR "human immunodeficiency virus" OR "human immune-deficiency virus" OR "human immuno-deficiency virus" OR "human immun* deficiency virus" OR aids OR "acquired immunodeficiency syndrome" OR "acquired immunodeficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR "acquired immun* deficiency syndrome")

Appendix 5. The Cochrane library search strategy

#1 MeSH descriptor HIV Infections explode all trees
#2 MeSH descriptor HIV explode all trees
hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME
#4 MeSH descriptor Lymphoma, AIDS-Related, this term only
#5 MeSH descriptor Sexually Transmitted Diseases, Viral, this term only
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Infectious Disease Transmission, Vertical, this term only
#8 mother-to-child OR MTCT OR mother-to-infant OR adult-to-child OR maternal-to-child OR vertical transmission OR perinatal transmission OR postnatal transmission OR post natal transmission OR maternal-infant transmission OR PMTCT
#9 (#7 OR #8)
#10 (#6 AND #9), from 1990 to 2010

Appendix 6. Controlled clinical trials search strategy

mother-to-child OR MTCT OR mother-to-child OR PMTCT OR postnatal transmission OR prenatal transmission OR vertical transmission OR HIV transmission OR mother-to-infant OR maternal-to-child OR maternal-infant | HIV OR HIV/AIDS

Appendix 7. ERIC search strategy

(mother-to-child OR MTCT OR mother-to-infant OR adult-to-child OR maternal-to-child OR vertical transmission OR perinatal transmission OR postnatal transmission OR post natal transmission OR maternal-infant transmission OR PMTCT) AND (HIV OR AIDS)

Appendix 8. EMBASE search strategy

#1 'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' OR 'b cell lymphoma'/de OR 'b cell lymphoma' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab
#2 'mother-to-child transmission' OR mtct OR 'mother-to-infant' OR 'adult-to-child' OR 'maternal-to-child' OR 'vertical transmission'/de OR 'vertical transmission' OR 'perinatal transmission' OR 'postnatal transmission' OR 'post natal transmission' OR 'maternal-infant transmission' OR pmtct OR 'disease transmission, vertical'/de OR 'disease transmission, vertical'
#3 #1 AND #2
#4 #1 AND #2 AND [humans]/lim AND [embase]/lim AND [1990-2010]/py

Appendix 9. Google Scholar search strategy

With at least one of the words: “mother-to-child” MTCT PMTCT “postnatal transmission” “prenatal transmission” “vertical transmission” “HIV transmission” “mother to infant” “maternal to child” “maternal-infant”

Appendix 10. MEDLINE search strategy

#1 Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR “sexually transmitted diseases, viral:noexp”[MH]
#2 Search mother-to-child[tiab] OR MTCT[tiab] OR mother-to-infant[tiab] OR adult-to-child[tiab] OR maternal-to-child[tiab] OR vertical transmission[tiab] OR perinatal transmission[tiab] OR postnatal transmission[tiab] OR post natal transmission[tiab] OR maternal-infant transmission[tiab] OR PMTCT[tiab] OR infectious disease transmission, vertical/prevention and control[mh]
#3 Search #4 AND #5
#4 Search (#4 AND #5) NOT (animals[mh] NOT humans[mh])
#5 Search (#4 AND #5) NOT (animals[mh] NOT humans[mh]) Limits: Publication Date from 1990/01/01 to 2010/07/26

Appendix 11. New York Academy of Medicine Grey Literature Collection

Mother-to-child
“mother-to-child” returned 172 results.
“kw,wrdl: mother-to-child and kw,wrdl: hiv yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 23 results
Mother to child
“Mother to child” returned 319 results
“kw,wrdl: mother-to-child and kw,wrdl: hiv yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 45 results
MTCT
“mtct ” returned 5 results
“kw,wrdl: mtct yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 2 results
PMTCT
“pmtct ” returned 2 results
“kw,wrdl: pmtct yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 2 results
Postnatal transmission
No results match your search for “postnatal transmission” in The New York Academy of Medicine Library Catalog
Prenatal transmission
“prenatal transmission ” returned 2 results
“kw,wrdl: prenatal transmission yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 2 results
Vertical transmission
“Vertical transmission” returned 7 results
“kw,wrdl: vertical transmission yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 7 results
HIV transmission
“hiv transmission ” returned 89 results
“kw,wrdl: hiv transmission yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 69 results
Mother-to-infant
“mother-to-infant” returned 63 results
“kw,wrdl: mother-to-infant and kw,wrdl: hiv yr,st-numeric,ge=1990 and yr,st-numeric,le=2010” returned 7 results
Maternal-to-child
“maternal-to-child” returned 132 results
“kw,wrdl: maternal-to-child and kw,wrdl: hiv yr,st-numeric,ge=1990 and yr,st-numeric,le=2010”
returned 20 results

Appendix 12. OpenSIGLE search strategy

("mother-to-child" OR MTCT OR "mother-to-child" OR PMTCT OR "postnatal transmission" OR "prenataltransmission" OR vertical transmission OR transmission OR "mother-to-infant" OR "maternal-to-child" OR"maternal-infant") AND (HIV OR AIDS)

Appendix 13. POPLINE search strategy

TITLE/KEYWORDS (mother-to-child transmission / MTCT / prevention of mother-to-child transmission / PMTCT / postnatal transmission / prenatal transmission / perinatal transmission / vertical transmission / HIV transmission / mother-to-infant / maternal-to-child / maternal-infant) & (HIV/AIDS)

Appendix 14. ProQuest Dissertations and Theses Database search startegy

(mother-to-child OR MTCT OR mother-to-child OR PMTCT OR postnatal transmission OR prenatal transmission OR vertical transmission OR mother-to-infant OR maternal-to-child OR maternal-infant) AND (HIV OR AIDS)

Appendix 15. PsycINFO search strategy

(HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV infect* OR human immunodeficiency virus OR human immunedeficiency virus OR human immune-deficiency virus OR human immuno-deficiency virus OR human immun* deficiency virus OR acquired immunodeficiency syndrome OR acquired immunedeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR acquired immun* deficiency syndrome) AND (mother-to-child OR MTCT OR mother-to-infant OR adult-to-child OR maternal-to-child OR vertical transmission OR perinatal transmission OR postnatal transmission OR post natal transmission OR maternal-infant transmission OR PMTCT)

Appendix 16. Sociological Abstracts search strategy

(mother-to-child OR MTCT OR mother-to-infant OR adult-to-child OR maternal-to-child OR vertical transmission OR perinatal transmission OR postnatal transmission OR post natal transmission OR maternal-infant transmission OR PMTCT) AND (HIV OR AIDS)

Appendix 17. U.S. National Library of Medicines (NLM) Gateway system search strategy

Search Strategy 1 (1990 - 2000)
#1 ("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])
#2 Search mother-to-child[tw] OR MTCT[tw] OR mother-to-infant[tw] OR adult-to-child[tw] OR maternal-to-child[tw] OR vertical transmission[tw] OR perinatal transmission[tw] OR postnatal transmission[tw] OR post natal transmission[tw] OR maternal-infant transmission[tw] OR PMTCT[tw] OR infectious disease transmission, vertical/prevention and control[mh] #3 Search: ((("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])) AND (Search mother-to-child[tw] OR MTCT[tw] OR mother-to-infant[tw] OR adult-to-child[tw] OR maternal-to-child[tw] OR

vertical transmission[tw] OR perinatal transmission[tw] OR postnatal transmission[tw] OR post natal transmission[tw] OR maternal-infant transmission[tw] OR PMTCT[tw] OR infectious disease transmission, vertical/prevention and control[mh])) NOT (animals[mh] NOT humans[mh]) Limit: 1990/01/01:2000/12/31
Search Strategy 2 (2001 - 2005)
#1 ("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])
#2 Search mother-to-child[tw] OR MTCT[tw] OR mother-to-infant[tw] OR adult-to-child[tw] OR maternal-to-child[tw] OR vertical transmission[tw] OR perinatal transmission[tw] OR postnatal transmission[tw] OR post natal transmission[tw] OR maternal-infant transmission[tw] OR PMTCT[tw] OR infectious disease transmission, vertical/prevention and control[mh]
#3 ((("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])) AND (Search mother-to-child[tw] OR MTCT[tw] OR mother-to-infant[tw] OR adult-to-child[tw] OR maternal-to-child[tw] OR vertical transmission[tw] OR perinatal transmission[tw] OR postnatal transmission[tw] OR post natal transmission[tw] OR maternal-infant transmission[tw] OR PMTCT[tw] OR infectious disease transmission, vertical/prevention and control[mh])) NOT (animals[mh] NOT humans[mh]) Limit: 2001/01/01:2005/12/31
Search Strategy 3 (2006 - 2010)
#1 ("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])
#2 Search mother-to-child[tw] OR MTCT[tw] OR mother-to-infant[tw] OR adult-to-child[tw] OR maternal-to-child[tw] OR vertical transmission[tw] OR perinatal transmission[tw] OR postnatal transmission[tw] OR post natal transmission[tw] OR maternal-infant transmission[tw] OR PMTCT[tw] OR infectious disease transmission, vertical/prevention and control[mh]
#3 ((("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])) AND (Search mother-to-child[tw] OR MTCT[tw] OR mother-to-infant[tw] OR adult-to-child[tw] OR maternal-to-child[tw] OR vertical transmission[tw] OR perinatal transmission[tw] OR postnatal transmission[tw] OR post natal transmission[tw] OR maternal-infant transmission[tw] OR PMTCT[tw] OR infectious disease transmission, vertical/prevention and control[mh])) NOT (animals[mh] NOT humans[mh]) Limit: 2001/01/01:2005/12/31

Appendix 18. WHO Global Health Library search strategy

(HIV OR AIDS) AND (mother-to-child OR MTCT OR mother-to-child OR PMTCT OR postnatal transmission OR prenatal transmission OR vertical transmission OR HIV transmission OR mother-to-infant OR maternal-to-child OR maternal-infant)

Appendix 19. WHO International Clinical Trials Registry Platform (WHO ICTRP) search strategy

(mother-to-child OR MTCT OR mother-to-child OR PMTCT OR postnatal transmission OR prenatal transmission OR vertical transmission OR HIV transmission OR mother-to-infant OR maternal-to-child OR maternal-infant) in TITLE AND (HIV OR HIV/AIDS) in CONDITIONAND DATE OF REGISTRATION is between (01/01/1990-27/07/2010)

HISTORY

Protocol first published: Issue 10, 2010

Review first published: Issue 6, 2011

CONTRIBUTIONS OF AUTHORS

RA conceived the idea for the review. LTC wrote the review. LTC, HE, MvV and SB performed the study selection process. LTC and HE extracted the data. LTC and MvV assessed the study for risk of bias. JC, RA and AM supervised the production and together with MvV, SB and HE provided comments on the drafts of the review.

DECLARATIONS OF INTEREST

None to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The Global Fund to Fight AIDS,Tuberculosis and Malaria, Switzerland.

The review received a partial financial contribution from The Global Fund to Fight AIDS, Tuberculosis and Malaria.

- The Department of Primary Care and Public Health, Imperial College London, Not specified.

The review received a partial financial contribution from The Department of Primary Care and Public Health, Imperial College London. The Department of Primary Care & Public Health at Imperial College is grateful for support from the NIHR Collaboration for Leadership in Applied Health Research & Care (CLAHRC) Scheme, the NIHR Biomedical Research Centre scheme, and the Imperial Centre for Patient Safety and Service Quality.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are a number of differences between the protocol and the review. These differences are mainly in the data analysis section, and are a consequence of the low number of included studies. Future updates of the review should consider incorporating these methods in case new studies are included.

Assessment of risk of bias in included studies

The initial assessment of methodology and the quality of evidence and data extraction was independently performed by two review authors. Any disagreements were resolved by discussion. Studies were assessed in accordance with the "risk of bias" tool described in the Cochrane Handbook for Systematic Reviews of Interventions and additional criteria developed by the Cochrane Effective Practice and Organisation of Care Group (EPOC) Group (Higgins 2008; EPOC 2002).

1. If we had found eligible RCTs and CCTs, we would have assessed them for risk of bias using the Cochrane Handbook tool which consists of the six following domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential biases. The assessment would also incorporate three additional domains that are recommended by the Cochrane EPOC group: imbalance of outcome measures at baseline; comparability of intervention and control group characteristics at baseline; and protection against contamination (Higgins 2008; EPOC 2002). As recommended by the Cochrane EPOC group, these criterions would have been used also for the evaluation of risk of bias for CBAs (EPOC 2002).

2. The included ITS studies would have been be assessed for potential bias, using the following seven domains: intervention independent of other changes; shape of intervention effect pre-specified; intervention unlikely to affect data collection; blinding of outcome assessors to intervention allocation; incomplete outcome data; selective outcome reporting; and other sources of bias (EPOC 1998).

3.The quality of evidence would have been evaluated using the GRADE approach (Guyatt 2008).

4. Review Manager would have been used to analyse data. We would have analyse the data using the intention-to-treat principle. The data would have been summarised statistically if available, of sufficient quality and sufficiently similar. Dichotomous data would have been calculated as relative risk (RR) with 95% confidence intervals (95% CIs). We would have calculated the mean difference and the weighted mean difference (WMD) with 95% CI for continuous outcomes. The overall results would have been calculated based on a fixed, or if heterogeneity is detected and it is appropriate to combine the trials, random-effects model.

5. In case we would have found missing data, we would contact the authors of the primary studies. The attrition rates for the outcomes of the included studies would have been presented in the review. We would not have performed the imputations for missing outcome data.

6. Heterogeneity of the studies would have been tested using the I^2 statistic with significance set at >50% and the chi-squared statistic with significance set at P<0.10. A forest plot would have been designed to present and examine the amount of data variation at a glance. Possible sources of heterogeneity would have been assessed by subgroup and sensitivity analysis Higgins 2003.

7. To examine if there are any reporting biases, we would have used funnel plots and tests for funnel plot asymmetry (Sterne 2008).

8. If possible, we would have performed sub-group analyses for low- and middle-income countries (World Bank 2010), integration with different health services, integration at single point vs. referral system, integration with different levels of service delivery.

9. Sensitivity analyses would have been performed to evaluate the potential impact of the study quality and design, low statistical power studies, unpublished studies and studies in languages other than English on effect size.

INDEX TERMS

Medical Subject Headings (MeSH)

*Developing Countries; *Program Development; Anti-HIV Agents [therapeutic use]; HIV Infections [prevention & control; *transmission]; Infectious Disease Transmission, Vertical [*prevention & control]; Nevirapine [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy