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Treatment of Kaposi sarcoma in children with HIV-1 infection (Review)

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[Intervention Review]

Treatment of Kaposi sarcoma in children with HIV-1 infection

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ABSTRACT

Background

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

Objectives

To describe the efficacy and effectiveness of current treatment options for HIV-associated KS in ART-treated paediatric populations.

Search methods

We used standard Cochrane methods to search electronic databases and conference proceedings with relevant search terms without limits to language.

Selection criteria

Randomised controlled trials, cohort studies, and case-control studies of HIV-infected infants and children <18 years old treated with ART and diagnosed with KS.

Data collection and analysis

Abstracts of all studies identified by electronic or bibliographic scanning were examined independently by two authors. We initially identified 920 references and examined 15 in detail for study eligibility. Data were abstracted independently using a standardised abstraction form.

Main results

After initially screening 920 titles, 15 full-text articles were closely examined by two authors. We identified four cohort studies that met our inclusion criteria for data extraction, coding, and potential meta-analysis.

Using the Newcastle-Ottawa Scale and Cochrane risk of bias assessments, all observational studies had cohorts that were representative of average (treated and untreated) HIV-infected children with Kaposi sarcoma. For all outcomes of interest, no study adjusted for any other potential confounders. Two of four observational studies either explicitly described complete follow up of the study participants and/or described the characteristics of the participants lost to follow up.

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The use of ART together with a chemotherapeutic regimen versus ART alone appears to increase the likelihood of KS remission in HIV-infected children diagnosed with KS, although data are sparse and not adequately adjusted for staging of disease and comorbidities. Additionally, though data are sparse, the use of ART together with a chemotherapeutic regimen versus chemotherapy alone in some analyses appears to increase the likelihood of KS remission and reduce the risk of death in HIV-infected children diagnosed with KS.

In this analysis, we found that the quality of evidence was very low due to small sample sizes and a paucity of paediatric literature.

Authors' conclusions

Data describing the efficacy of different treatment options for pediatric KS, to include chemotherapy and ART, are sparse. However, the use of ART together with a chemotherapy regimen may be superior to the use of ART alone or of chemotherapy alone.

PLAIN LANGUAGE SUMMARY

Treatment of Kaposi sarcoma in children with HIV-1 infection

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

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Summary of findings for the main comparison. Combination Chemotherapy + ART compared to Single Agent Chemotherapy + ART for Kaposi sarcoma in children with HIV-1 infection

Combination Chemotherapy + ART compared to Single Agent Chemotherapy + ART for Kaposi sarcoma in children with HIV-1 infection

Patient or population: Kaposi sarcoma in children with HIV-1 infection
Settings:
Intervention: Combination Chemotherapy + ART
Comparison: Single Agent Chemotherapy + ART

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Single Agent Chemotherapy + ART	Combination Chemotherapy + ART				
Mortality	Study population		RR 0.38 (0.24 to 0.58)	50 (1 Studies)	⊕⊝⊝⊝ VERY LOW	
	14/14 (100.0)%	380 per 1000 (240 to 580)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No explanation was provided
[2]Unadjusted Estimates

Summary of findings 2. Vincristine + ART compared to Bleomycin + vincristine + ART for Kaposi sarcoma in children with HIV-1 infection

Vincristine + ART compared to Bleomycin + vincristine + ART for Kaposi sarcoma in children with HIV-1 infection

Patient or population: Kaposi sarcoma in children with HIV-1 infection

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Settings:
Intervention: Vincristine + ART
Comparison: Bleomycin + vincristine + ART

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Bleomycin + vincristine + ART	Vincristine + ART				
Complete: Vincristine+ART vs Bleomycin+vincristine+ART	Study population		RR 0.69 (0.33 to 1.47)	26 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	13/18 (72.2)%	498 per 1000 (238 to 1062)				
Complete/Partial: Vincristine+ART vs Bleomycin+vincristine+ART	Study population		RR 0.79 (0.52 to 1.2)	26 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	17/18 (94.4)%	746 per 1000 (491 to 1133)				
Complete: Vincristine+ART vs Bleomycin+vincristine+ART	Study population		RR 0.92 (0.49 to 1.74)	24 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	13/18 (72.2)%	664 per 1000 (354 to 1257)				
Complete/Partial: Vincristine+ART vs Bleomycin+vincristine+ART	Study population		RR 1.01 (0.79 to 1.29)	24 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	17/18 (94.4)%	954 per 1000 (746 to 1218)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No explanation was provided
[2]Many patients had missing outcome data
[3]Unadjusted estimates

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[4]Very few cases (< 50)

Summary of findings 3. ART alone compared to Vincristine or Bleomycin for Kaposi sarcoma in children with HIV-1 infection

ART alone compared to Vincristine or Bleomycin for Kaposi sarcoma in children with HIV-1 infection

Patient or population: Kaposi sarcoma in children with HIV-1 infection
Settings:
Intervention: ART alone
Comparison: Vincristine or Bleomycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Vincristine or Bleomycin	ART alone				
Complete Response	Study population		RR 1.2 (0.13 to 11.43)	24 (1 Studies)	⊕⊝⊝⊝ VERY LOW	
	1/9 (11.1)%	133 per 1000 (14 to 1270)				
Complete or Partial Response	Study population		RR 0.2 (0.05 to 0.79)	24 (1 Studies)	⊕⊝⊝⊝ VERY LOW	
	6/9 (66.7)%	133 per 1000 (33 to 527)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No explanation was provided
[2]Unadjusted Estimates
[3]<50 cases

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Summary of findings 4. Chemotherapy + ART compared to ART for Kaposi sarcoma in children with HIV-1 infection

Chemotherapy + ART compared to ART for Kaposi sarcoma in children with HIV-1 infection

Patient or population: Kaposi sarcoma in children with HIV-1 infection
Settings:
Intervention: Chemotherapy + ART
Comparison: ART

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ART	Chemotherapy + ART				
Complete Response to Tx	Study population		RR 1.57 (0.22 to 11.34)	89 (2 Studies)	⊕⊖⊖⊖ VERY LOW	
	9/27 (33.3)%	523 per 1000 (73 to 3780)				
Complete/Partial Response to Tx	Study population		RR 5.75 (1.59 to 20.73)	39 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	2/13 (15.4)%	885 per 1000 (245 to 3189)				
Complete Among Known Outcome	Study population		RR 0.84 (0.48 to 1.48)	26 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	2/2 (100.0)%	840 per 1000 (480 to 1480)				
Complete/Partial Among Known Outcome	Study population		RR 1.13 (0.67 to 1.89)	26 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	2/2 (100.0)%	1130 per 1000 (670 to 1890)				
Mean CD4% Increase During Chemo	24	The mean Mean CD4% Increase During Chemo in the intervention group was MD 13.2 higher (1.75 higher to 24.65 higher)	-	48 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
Mortality	Study population		RR 0.72 (0.37 to 1.43)	50 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	7/14 (50.0)%	360 per 1000 (185 to 715)				

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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No explanation was provided
[2]Very few cases (< 50)
[3]Unadjusted estimates
[4]Many patients had missing outcome data

Summary of findings 5. Chemotherapy + ART compared to Chemotherapy Alone for Kaposi sarcoma in children with HIV-1 infection

Chemotherapy + ART compared to Chemotherapy Alone for Kaposi sarcoma in children with HIV-1 infection

Patient or population: Kaposi sarcoma in children with HIV-1 infection
Settings:
Intervention: Chemotherapy + ART
Comparison: Chemotherapy Alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy Alone	Chemotherapy + ART				
Complete Response to Tx	Study population		RR 6.54 (1 to 42.86)	36 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	1/10 (10.0)%	654 per 1000 (100 to 4286)				
Complete/Partial Response to Tx	Study population		RR 1.47 (0.87 to 2.49)	36 (1 Studies)	⊕⊖⊖⊖ VERY LOW	
	6/10 (60.0)%	882 per 1000 (522 to 1494)				
Complete Among Known Outcome	Study population		RR 4.25 (0.7 to 25.91)	30 (1 Studies)	⊕⊖⊖⊖ VERY LOW	

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	1/6 (16.7)%	708 per 1000 (117 to 4318)			
Complete/Partial Among Known Outcome	Study population		RR 1.01 (0.81 to 1.27)	30 (1 Studies)	⊕⊝⊝⊝ VERY LOW
	6/6 (100.0)%	1010 per 1000 (810 to 1270)			
Mortality	Study population		RR 0.46 (0.29 to 0.73)	98 (2 Studies)	⊕⊝⊝⊝ VERY LOW
	22/32 (68.8)%	316 per 1000 (199 to 502)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No explanation was provided
[2]Unadjusted estimate
[3]Many patients had missing outcome data
[4]Very few cases (< 50)
[5]Imputed data from information in text for one study. Data not used in calculating RR

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BACKGROUND

Even in the era of antiretroviral therapy (ART), Kaposi sarcoma (KS) remains the second most frequent HIV-related malignancy (HRM) worldwide and the most common HRM in sub-Saharan Africa where HIV is most prevalent and human herpesvirus 8 (HHV-8), the precipitating agent for the development of KS, is endemic (Martellotta 2009). Arising from HHV-8-infected lymphatic endothelial cells, KS is characterized by four distinct clinical variants: classic KS, endemic KS, immune suppression-associated KS and epidemic or AIDS-associated KS (Antman 2000). Rates of HHV-8 infection in the adult population in certain parts of East Africa are as high as 90% (Sarmati 2004). In children, prevalence of HHV-8 infection ranges from 25-60% throughout East and Central Africa (Sarmati 2004; Kasolo 2007). In contrast, prevalence in high-income countries is substantially less, with prevalence of <3% in the United States and Northern Europe (Martro 2004). Due to the low incidence of paediatric KS in high-income countries, characterization of paediatric KS in the ART-era remains incomplete. In adults, KS is an aggressive disease among individuals with advanced HIV infection and a low absolute CD4 count (Martellotta 2009). Compared to adults, however, presentation and outcome of KS in children may be quite different, posing questions about proper staging and treatment of paediatric KS, which up to now has been based on experience with adult patients and utilizing the TIS system first proposed by Krown et al (Krown 1989).

Gantt et al showed in Ugandan children with HIV-associated KS that a distinct presentation with lymphadenopathic KS occurred in younger children with higher CD4 counts, an uncommon presentation in adults. Response was also quite favourable as compared to adult data (62.5% with complete response of those receiving ART and/or chemotherapy) (Gantt 2010). These results contrast with those of Stefan et al who studied South African children and did not find lymph node involvement, higher CD4 counts at diagnosis, or improved outcomes (40% survival rate at 16 months)(Stefan 2011). No uniform paediatric staging criteria or treatment regimen have been prospectively studied in the literature; consensus guidelines recommend consideration of multiple different treatment regimens (Molyneux 2013). Adult guidelines recommend first-line usage of liposomal doxorubicin, an expensive chemotherapeutic agent not readily available or sustainable in low- and middle-income countries (Cooley 2007, Di Lorenzo 2007, Raimundo 2013). Paediatric evidence supporting the use of liposomal doxorubicin as a first-line agent is lacking. Additionally, evidence in adults is unclear as to whether alternative regimens, including bleomycin, vincristine and doxorubicin, are truly inferior to liposomal doxorubicin (Di Lorenzo 2007).

Description of the condition

KS is a malignancy of the endothelial cells of blood vessels. AIDS-related KS can be quite variable in presentation, especially in children. Skin-related lesions tend to involve the face, extremities and groin though may be present anywhere on the skin.These lesions can be macular or nodular and may be hyperpigmented, purplish or flesh-colored. Similar lesions are often seen on the upper palate and gums. Associated dissemination to lymphatics may occur, resulting in painful lymphoedema with hard, often tender swelling of lymph nodes as well as in the extremities, face and groin due to congestion of the lymphatic drainage system. Due to this congestion patients uniquely have a hard oedema rather than the pitting oedema of volume overload; this oedema is often described as "woody". Skin lesions without lymph involvement are often asymptomatic. Visceral involvement may also be possible and represents systemic disease. KS can be in any organ but typically involves the lungs (often with associated pleural effusion) and liver. Involvement of the pericardium has also been reported. Systemic involvement may be quite symptomatic with pulmonary or abdominal involvement, or KS may be an incidental finding (Di Lorenzo 2007).

Description of the intervention

Many patients may benefit from systemic chemotherapy in addition to the initiation of ART. As paediatric staging and treatment criteria are not readily available, uniformity in treatment does not exist. In general, most practitioners will give systemic chemotherapy to those patients with extensive skin involvement or disseminated or systemic disease (Mosam 2012; Bower 2014). Multiple potential systemic chemotherapeutic regimens exist, which have been mainly studied in adults. These include single-agent liposomal doxorubicin, combination chemotherapy with bleomycin, vincristine and doxorubicin, as well as single-agent paclitaxel. Additional therapy with non-chemotherapeutic agents, such as interferon alfa, have also been reported. For those with less extensive skin involvement, ART alone is usually sufficient to cause lesion regression; if this fails, chemotherapy remains a future option (Mosam 2012; Bower 2014). Finally, for those patients with symptomatic local disease, local therapies such as radiotherapy, intralesional chemotherapy, cryotherapy, surgery, topical therapy and laser and photodynamic treatment have all been reported (Di Lorenzo 2007).

OBJECTIVES

This review aims to describe the efficacy and effectiveness of current treatment options for HIV-associated KS in ART-treated paediatric populations.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)
- Observational studies with comparison groups (e.g., cohort studies)

We chose to include observational studies for multiple reasons. First, RCTs were not expected to be commonly performed because it would likely be unethical to restrict presumed efficacious treatment to HIV-infected children. Additionally, we did not anticipate a large body of data and we wanted to be less restrictive in gathering the evidence.

Types of participants

- HIV-infected infants and children <18 years old treated with ART who have been diagnosed with KS

Types of interventions

- ART plus antineoplastic therapy
- ART alone
- Antineoplastic therapy alone

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For purposes of this review antineoplastic therapy includes:

- For extensive skin involvement or disseminated or systemic disease, systemic chemotherapy including: single-agent liposomal doxorubicin; combination chemotherapy with bleomycin, vincristine and doxorubicin; and single-agent paclitaxel
- Non-chemotherapeutic agents including: interferon alfa
- For symptomatic local disease, local therapies including: radiotherapy, intralesional chemotherapy, cryotherapy, surgery, topical therapy and laser and photodynamic treatment

Types of outcome measures

The following are the outcomes of interest we extracted for included studies. However, if a study did not have relevant outcome data but still satisfied our inclusion criteria, we would include it for descriptive purposes.

Primary outcomes

- Death
- Treatment response
- Duration of response

Secondary outcomes

- Opportunistic infections
- Adverse events

Search methods for identification of studies

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

Electronic searches

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

We searched the following electronic databases, in the period from 01 January 1980 to the search date (06 January 2014):

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

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

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

Conference databases

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

- British HIV/AIDS Association, 2001-2010
- Conference on Retroviruses and Opportunistic Infections (CROI), 1994-2008
- European AIDS Society Conference, 2001 and 2003
- International AIDS Society, International AIDS Conference (IAC), 1985-2006
- International AIDS Society, Conference on HIV Pathogenesis, Treatment and Prevention (IAS), 2001-2005
- US National HIV Prevention Conference, 1999, 2001, 2003, 2005, 2007, 2009, and 2011

We also searched the CROI and International AIDS Society web sites for abstracts presented at conferences subsequent to those listed above (CROI, 2009-2013; IAC, 2008-2012; IAS, 2007-2013).

Searching other resources

In addition to searching electronic databases, we contacted individual researchers, experts working in the field and authors of major trials to address whether any relevant manuscripts are in preparation or in press. The references of published articles found in the above databases were searched for additional pertinent materials. We searched WHO's International Clinical Trials Registry Platform (ICTRP) and www.clinicaltrials.gov to identify ongoing clinical trials.

Data collection and analysis

The methodology for data collection and analysis was based on the guidance of Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008).

Selection of studies

One author performed a broad first cut of all downloaded material from the electronic searches to exclude citations that are plainly irrelevant. Two authors read the titles, abstracts, and descriptor terms of the remaining downloaded citations to identify potentially eligible reports. Full text articles were obtained for all citations identified as potentially eligible and two authors independently inspected these to establish the relevance of the article according to the pre-specified criteria. Where there was uncertainty as to the eligibility of the record, the full article was obtained. Two authors independently applied the inclusion criteria, and any differences arising were resolved by discussion with a neutral arbiter. Studies were reviewed for relevance based on study design, types of participants, and outcome measures. Studies were included irrespective of their publication status if we were able to identify and obtain unpublished data.

Data extraction and management

Two authors independently extracted data into a standardised, pre-tested data extraction form. The following characteristics were extracted from each included study:

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

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the bias assessment tool described in the Cochrane Handbook (Higgins 2008). We resolved any disagreement by discussion or by involving a neutral third party to adjudicate. The Cochrane approach assesses risk of bias in individual studies across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases.

Sequence generation (checking for selection bias)

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

Allocation concealment (checking for selection bias)

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

Blinding (checking for performance bias and detection bias)

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

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

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

Selective reporting

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

Other forms of bias

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

For blinding and incomplete outcome data, multiple entries can be made if more than one outcome (or time points) is involved.

We used the Newcastle-Ottawa Scale (Newcastle-Ottawa) to assess the quality and risk of bias in non-randomised studies. Specifically, the scale uses a star system to judge three general areas: selection of study groups, comparability of groups, and ascertainment of outcomes (in the case of cohort studies). As a result, this instrument can assess the quality of non-randomised studies so that they can be used in a meta-analysis or systematic review. Please see Figure 1 and Appendix 2 for details.

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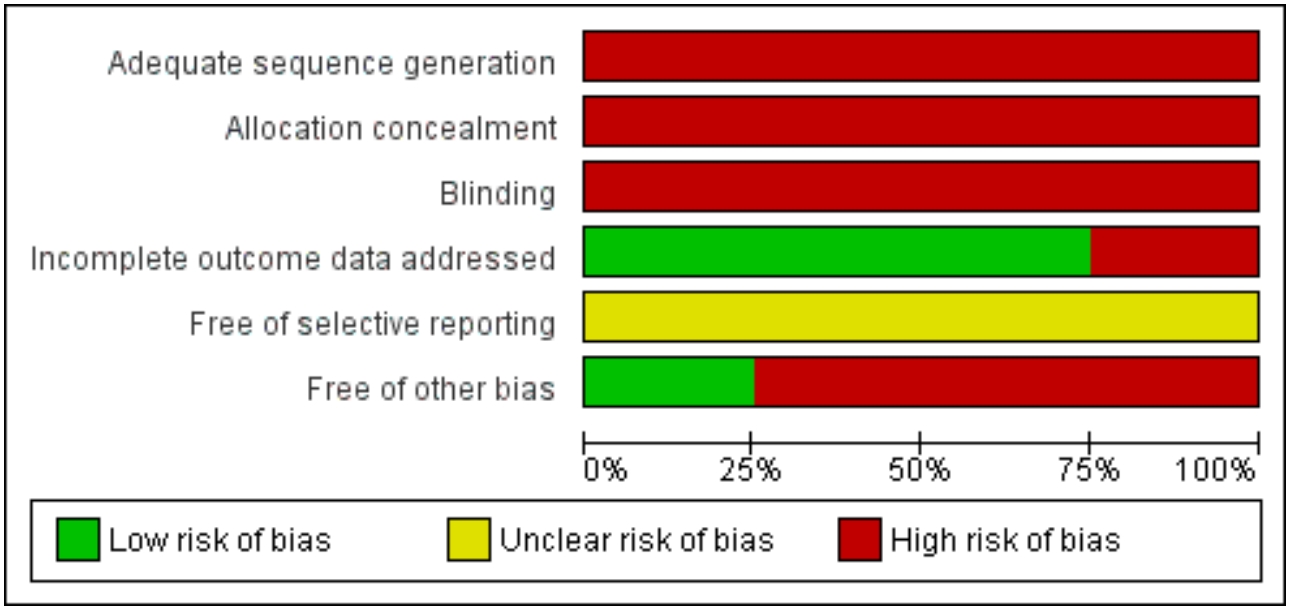
Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



The quality of evidence across the body of evidence was assessed with the GRADE approach (Guyatt 2008), which defines the quality of evidence for each outcome as"the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest" (Higgins 2008). The quality rating across studies has four levels: high, moderate, low, or very low. Randomised trials are considered to be of high quality, but can be downgraded for any of five reasons; similarly, observational studies are considered to be of low quality, but can be upgraded for any of 3 reasons. The 5 factors that decrease the quality of evidence are: 1) limitations in study design; 2) indirectness of evidence; 3) unexplained heterogeneity or inconsistency of results; 4) imprecision of results; or 5) high probability of publication bias. The three factors that can increase the quality level of a body of evidence are: 1) large magnitude of effect; 2) if all plausible confounding would reduce a demonstrated effect; and 3) if there is a dose-response gradient.

Measures of treatment effect

We extracted the unadjusted relative risk (RR) for dichotomous outcomes and the 95% confidence interval (CI). For continuous data we calculated a weighted mean difference (WMD). When data were not presented in the paper, we calculated RR and WMD.

Dealing with missing data

We contacted study authors if it was necessary to obtain data missing from published reports.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (I^2 greater than 50%), we explored potential reasons for the heterogeneity.

Assessment of reporting biases

Where we suspected reporting bias we attempted to contact study authors and ask them to provide missing outcome data.

Data synthesis

Meta-analysis was conducted, when appropriate. Both fixed effects and random effects models were used in the analysis; if there were discrepancies between the models, we explored potential reasons for the differences. If meta-analysis was not possible, a narrative synthesis of a particular intervention was undertaken. We also examined data using the GRADEpro software (GRADEpro 2008). GRADE evidence profiles and summary of findings tables were generated.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was explored by analyses per subgroup, which was performed for populations or types of interventions that are dissimilar in a meaningful way. These analyses could include subgroup analyses based on the stage of the epidemic in the study region, higher-income vs. low- or middle-income country, characteristics of key populations, or other factors. Specifically, we aimed to examine the effects of interventions on KS outcomes among disease staging subgroups.

RESULTS

Description of studies

Results of the search

Searches were conducted on January 06, 2014, and produced 920 titles after duplicates were removed (Figure 2). After initial screening of titles, 15 titles and abstracts were selected for further review by two authors (AA and AKA). AA and AKA independently conducted the selection of potentially relevant studies by scanning the titles, abstracts, and descriptor terms of all downloaded material from the electronic searches. Irrelevant reports were

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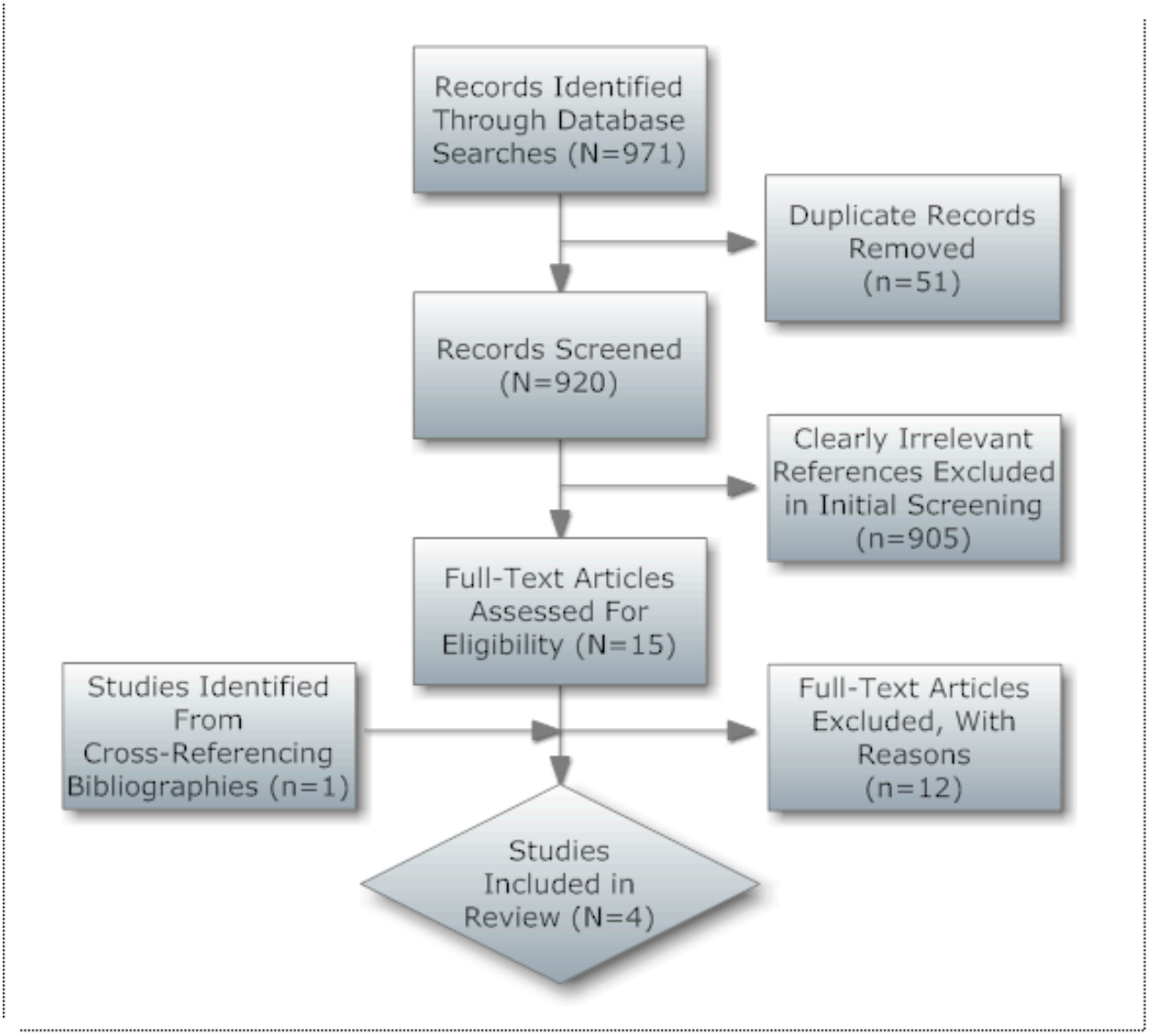
discarded, and the full article was obtained for all potentially relevant or uncertain reports. AA and GWR independently applied the inclusion criteria. GWR acted as arbiter where there was disagreement. Studies were reviewed for relevance, based on study design, types of participants, exposures and outcomes measures. Finally, where resolution was not possible because further information was required, the study was allocated to the list of those awaiting assessment. Attempts to contact authors to provide further clarification of data are ongoing. We did not identify unpublished studies for inclusion.

Figure 2. Study Flow Diagram



Fifteen full-text articles were closely examined by two authors (AA and AKA). We identified four cohort studies that met our inclusion criteria for data extraction, coding, and potential meta-analysis.

Included studies

No randomised controlled trial was identified. The four included cohort studies were conducted in Malawi (Cox 2013), Uganda (Gantt 2010), South Africa (Stefan 2011) and Mozambique (Vaz 2011). All four cohort studies retrospectively analysed data from medical charts of hospitalized children at a cancer institute or hospital.

Three of the studies did not specifically identify the regimens or drug combinations that defined ART use. However, chemotherapy was defined as any combination of bleomycin (Cox 2013; Stefan 2011 and Gantt 2010), vincristine (Cox 2013; Stefan 2011 and Gantt 2010), paclitaxel (Vaz 2011) and/or doxorubicin (Cox 2013 and Stefan 2011). Cox et al reported that among 76 patients who began ART, 64 (84%) started fixed dose combination therapy of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), 2 (3%) started ART consisting of zidovudine (ZDV), 3TC and either NVP or efavirenz (EFV), and 4 (5%) started ART consisting of d4T, 3TC, and EFV. The remaining 6 (8%) patients who were treated with ART started a protease inhibitor-based regimen (Cox 2013).

Cox 2013: Cox et al conducted a retrospective cohort study in Malawi and Botswana. The researchers followed a cohort of 81 HIV-

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infected children diagnosed with KS at the Baylor Children's Clinical Centres of Excellence from 2003 to 2009. The median age of patients was 8.0 years (interquartile range [IQR] 5.1-11.3 years), and the median CD4 and CD4% at KS presentation were 297 cells/µL (IQR 85-526) and 12.4% (IQR 4.3-18.6%), respectively. Of the 30 children alive at 12 months, 19 (63%) achieved complete remission and 11 (37%) achieved partial remission or stable disease.

Of the 69 children followed-up at 12 months, 39 (57%) died during follow-up, while 30 (43%) were known to be alive. Children who received chemotherapy and ART were significantly less likely to die than children who received chemotherapy alone (RR=0.44; 95% CI 0.23-0.85). Children who received chemotherapy and ART had the same risk of death as children who received ART alone (RR=0.72; 95% CI 0.37-1.43).

Staging of patients was performed, and multiple treatment regimens were utilized, though the authors do not describe associations between stage and treatment regimen utilized (treatment was based on country availability rather than stage). Staging was performed using the TIS staging system, and the staging was distributed as follows: 27 (34%) were T0 and 52 (66%) T1; 23 (30%) were I0 and 54 (70%) I1; and 8 (10%) were S0 and 69 (90%) were S1. In multivariable analyses, the patients staged at I1 were more likely to die than patients staged at I0 (adjusted OR= 4.29; 95% CI 1.27-14.55), but generally the authors concluded that TIS staging did not correlate well with outcomes. Among the 62 children treated with chemotherapy, 14 (23%) had documented side-effects. Specifically, 11% reported constipation or abdominal pain, 2% reported peripheral neuropathy, and 3% reported palmar hyperpigmentation.

Gantt 2010: Gantt et al conducted a retrospective cohort study in Uganda. They followed a cohort of 73 HIV-infected children with KS referred to a cancer institute in Kampala from 2004 to 2007. The median age of patients was 10.0 years (range 2-18 years), and the median CD4 and CD4% at KS presentation were 210 cells/µL and 7.4%, respectively. Of the 73 children, 20 (27.4%) achieved complete remission and 11 (15.1%) achieved partial remission. More than half (n=41) had missing remission outcome data. ART regimens included either a protease inhibitor (all lopinavir/ritonavir) or a non-nucleoside reverse transcriptase inhibitor (EFV or NVP). All ART regimens included 3TC in combination with TDF, d4T or ZDV.

Among all patients, complete remission was achieved in 17 (65.4%) of 26 children who received a chemotherapeutic regimen plus ART, compared to 2 (15.4%) of 13 children who received ART alone (RR=4.25; 95% CI 1.15-15.68). Comparing chemotherapy plus ART versus chemotherapy alone, children who received a chemotherapeutic regimen together with ART were significantly more likely to achieve complete remission compared to children who received only chemotherapy (17/26 children [65.4%] compared to 1/10 [10%], RR=6.54; 95% CI 1.00-42.86). Comparing specific chemotherapeutic regimens among all patients, complete remission was achieved in 4 (50.0%) of 8 children who received vincristine plus ART and 13 (72.2%) of 18 who received ART plus bleomycin and vincristine (RR=0.69; 95% CI 0.33-1.47). Considering only patients with known KS outcomes, 17 (70.8%) of 24 children who received both chemotherapy and ART achieved complete remission compared to 2 (100%) of 2 children who received ART alone (RR=0.84; 95% CI 0.48-1.48). and 1 (16.7%) of 6 who received chemotherapy alone (RR=4.25; 95% CI 0.70-27.91). Among children who received both ART and chemotherapy, complete remission was achieved in 4 (66.7%) of 6 who received vincristine plus ART and 13 (72.2%) of 18 children who received bleomycin and vincristine plus ART (RR=0.92; 95% CI 0.49-1.74).

Overall, complete or partial remission was achieved in 23 (88.5%) of 26 children who received a chemotherapeutic regimen plus ART, compared to 2 (15.4%) of 13 children who received ART alone (RR=5.75; 95% CI 1.59-20.73) and 6 (60.0%) of 10 children who received chemotherapy alone (RR=1.47; 95% CI 0.87-2.49). Complete or partial remission was achieved in 6 (75.0%) of 8 children who received vincristine plus ART and 17 (94.4%) of 18 children who received ART plus bleomycin and vincristine (RR=0.79; 95% CI 0.52-1.20). Twenty-three (95.8%) of 24 children who received both chemotherapy and ART achieved complete or partial remission compared to 2 (100%) of 2 children who received ART alone (RR=1.13; 95% CI 0.67-1.89) and 6 (100%) of 6 who received chemotherapy only (RR=1.01; 95% CI 0.81-1.27). Complete or partial remission was achieved in all 6 children who received vincristine plus ART and 17 (94.4%) of 18 children who received ART plus bleomycin and vincristine (RR=1.01; 95% CI 0.79-1.29).

No staging of patients was done and it is unclear whether patients with low stage (i.e., stage I disease) benefited from the addition of chemotherapy to ART. Additionally, there is no mention of toxicity from the chemotherapeutic treatment.

Stefan 2011: Stefan et al conducted a retrospective cohort study of 70 HIV-infected children with KS hospitalized in South Africa from 1998 to 2009. The mean age of patients was 73 months and the mean CD4 and CD4% at KS presentation were 440 cells/µL (SD=385) and 12.2% (SD=9.13%), respectively. Nearly all patients receiving ART regimens received EFV, d4T and 3TC (14/17). Of the 60 children for whom data on chemotherapy use was reported, 52 received chemotherapy and 8 did not. Of the 70 children, 32 (45.7%) died during follow-up, and 28 (40.0%) were known to be alive (10 of whom had progressive disease and 5 of whom were still on treatment). Children who received both chemotherapy and ART were less likely to die than children who received chemotherapy alone (RR=0.49; 95% CI 0.26-0.93).

Staging of patients was performed and multiple treatment regimens were utilized. However, the authors do not describe a clear association between stage and treatment regimen utilized (regimens used included vincristine only, bleomycin and vincristine and doxorubicin, bleomycin and vincristine). There is no mention of toxicity from the chemotherapeutic regimens. The KS staging of patients was distributed as follows: 20 (30.5%) were stage I or II, 19 (30.2%) were stage III, and 24 (38.1%) were stage IV, using a staging system which progressed from skin disease (stage I/II) to lymph node (stage III) to visceral involvement (stage IV). Seven patients had an undetermined stage.

Vaz 2011: Vaz et al conducted a retrospective cohort study in Mozambique of 28 HIV-infected children with KS hospitalized from 2003 to 2008 and followed for a median of 27 months (IQR=18-36 months). The mean age of patients was 8.3 years (range 2-16 years), and the median CD4% at KS presentation was 16% (IQR=9-22%). All children received ART for one month prior to the initiation of KS treatment with paclitaxel.

The authors note that none of the 28 children had an improvement without chemotherapy. Gradual disappearance of KS lesions was

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seen in all children by the end of their chemotherapy, leading to total remission 1-10 months after chemotherapy. Remission was sustained in all but 3 (10.7%) children during a median follow-up time of 27 months (IQR=20-36). The mean CD4% increased by 13.2% after introduction of chemotherapy (MD=13.2%; 95% CI 1.8-24.7%).

Staging of patients was performed utilizing the TIS staging system, and it appears that lower-stage patients did better than higher-stage patients. Specifically, of 15 patients with low-risk tumor staging, 13 (86.7%) achieved long-term remission. Of 13 patients with high-risk tumor staging, 6 (46.2%) achieved long-term remission. Additionally, the authors report some toxicity outcomes. Four patients had early deaths, and 4 died later, but none of these deaths appeared attributable to chemotherapy. Two patients were unable to complete the allotted treatment course secondary to myelosuppression. Grade 1 and 2 adverse events were limited to fatigue (n=5) and myalgia (n=3). Grade 3 and 4 adverse events were limited to anaemia (n=2), neutropoenia (n=2) and thrombocytopoenia (n=1).

Excluded studies

We excluded Davidson 2010 because it was a commentary in a journal and Niehues 1999 because it was a review paper of treatment options. Bunn 2008 was excluded because it was a review of care options and a case study of 3 KS reports. Ahmed 2012 was excluded for similar reasons.

Risk of bias in included studies

In addition to Cochrane Collaboration's tool for assessing the risk of bias for each individual study (Higgins 2008), we applied the Newcastle-Ottawa Scale for bias assessment within observational studies to all included observational studies (Newcastle-Ottawa). The risk of bias for the included observational studies was assessed on the data and outcomes published within the manuscripts. Please see Figure 1; Figure 3 and Appendix 2 for assessment results from the Newcastle-Ottawa Scale and Cochrane risk of bias assessments. All observational studies had cohorts that were representative of average, treated and untreated, HIV-infected children with Kaposi sarcoma. For all outcomes of interest, no study adjusted for any other potential confounders. Two of four observational studies either explicitly described complete follow up of the study participants and/or described the characteristics of the participants lost to follow up (Stefan 2011 and Vaz 2011).

Figure 3.

Summary of critical appraisal of included studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies

Study ID	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)
Cox et al (2013)	****	--	***
Stefan et al (2011)	****	--	***
Vaz et al (2011)	****	--	***
Gantt et al (2010)	****	--	**

Selection
1) Representativeness of intervention cohort—a] Truly representative of average, treated serodiscordant couple*; b] somewhat representative of average, treated, serodiscordant couple*; c] only selected group of patients; no description of derivation of cohort
2) Selection of non intervention cohort—a] drawn from same community as intervention cohort*; b] drawn from different source; c] no description of the derivation of the non intervention cohort
3) Ascertainment of intervention—a] health record*; b] structured interview*; c] written self-report; d] no description
4) Demonstration that outcome was not present at start of study—a] yes*; b] no
Comparability
1) Comparability of cohorts on basis of design or analysis—a] study controls for age, sex, or frequency of sex*; b] study controls for any additional factors*
Outcome
1) Assessment of outcome—a] independent blind assessment*; b] record linkage*; c] self report; d] no description
2) Was follow up long enough for outcomes to occur—a] yes (median duration of follow up >6 months)*; b] no
3) Adequacy of follow up of cohort—a] complete follow up*; b] minimal loss to follow up (<=20%); c] follow up rate < 80% and no description of losses to follow up; d] no statement

Effects of interventions

See: **Summary of findings for the main comparison** Combination Chemotherapy + ART compared to Single Agent Chemotherapy + ART for Kaposi sarcoma in children with HIV-1 infection; **Summary of findings 2** Vincristine + ART compared to Bleomycin + vincristine + ART for Kaposi sarcoma in children with HIV-1 infection; **Summary of findings 3** ART alone compared to Vincristine or Bleomycin for Kaposi sarcoma in children with HIV-1 infection; **Summary of findings 4** Chemotherapy + ART compared to ART for Kaposi sarcoma in children with HIV-1 infection; **Summary of findings 5** Chemotherapy + ART compared to Chemotherapy Alone for Kaposi sarcoma in children with HIV-1 infection

Chemotherapy + ART versus ART alone

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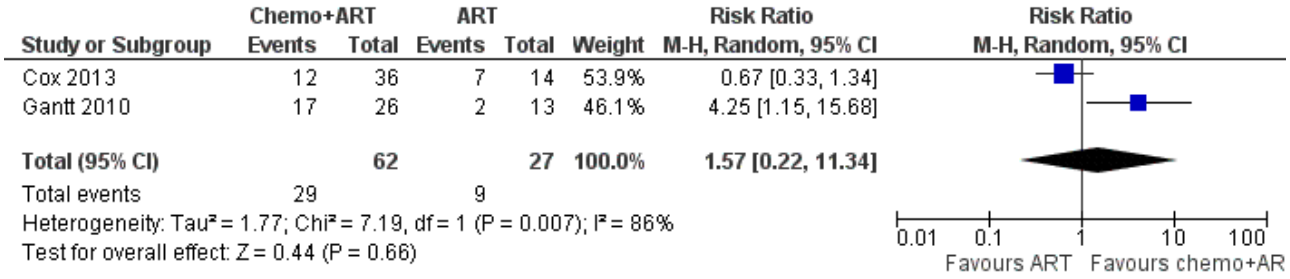
KS remission

Compared to the use of ART alone, the use of ART together with a chemotherapeutic regimen appears to increase the likelihood of KS remission and reduce the risk of death in HIV-infected children diagnosed with KS, although, as mentioned previously, staging is poorly delineated so it remains unclear how stage of disease plays into this association. We examined the association between receiving vincristine +/- bleomycin plus ART and ART alone for two outcomes -- complete remission and partial or complete remission. Assigning patients with unknown outcomes as not having achieved remission, children treated with chemotherapy plus ART had a higher unadjusted likelihood of complete KS remission than children treated only with ART (RR=4.25; 95% CI 1.15-15.68) (Gantt 2010). Similarly, assigning patients with unknown outcomes as not having achieved remission, 23 (88.5%) of 26 children treated with chemotherapy plus ART were in partial or complete KS remission compared to 2 (15.4%) of 13 children treated only with ART (RR=5.75; 95% CI 1.59-20.73) (Gantt 2010). When considering only patients with known outcomes, there was no difference in likelihood of complete KS remission between children treated with chemotherapy plus ART and children treated with ART alone (RR=0.84; 95% CI 0.48-1.48) (Gantt 2010). Similarly, when considering patients with known outcomes, there was no difference in likelihood of complete or partial KS remission between children treated with chemotherapy plus ART and children treated with ART alone (RR=1.13; 95% CI 0.67-1.89), though only 2 children treated with ART alone had known remission outcomes (Gantt 2010). Cox et al reported that 12 of 36 patients treated with combination chemotherapy and ART were in complete remission, while 7 of 14 children treated only with ART were in complete remission (RR=0.67; 95% CI 0.33-1.34) (Cox 2013). Pooling data from Cox et al and Gantt et al, the likelihood of complete remission was not significantly different between children treated with combination chemotherapy and ART versus ART alone (RR=1.57; 95% CI 0.22-11.34, I2=86%) (see Figure 4).

Figure 4. Forest plot of comparison: 1 Chemotherapy + ART vs ART, outcome: 1.1 Complete Response to Treatment.



Assigning patients with unknown outcomes to the no remission outcome, there was no difference in risk of complete remission between children who received ART alone (2/15 [13.3%] vs. 1/9 [11.1%]), and those who received vincristine or bleomycin alone (1 [11.1%] of 9 patients, RR=1.20; 95% CI 0.13-11.43) (Gantt 2010). However, children who received ART alone were significantly less likely to achieve complete remission compared to those who received vincristine or bleomycin (2/15 [13.3%] vs. 6/9 [66.7%], RR=0.20; 95% CI 0.05-0.79) (Gantt 2010). Only two children were treated with ART alone, obviating any analysis comparing them to other treatment regimens. Qualitatively, when considering only patients with known outcomes, 2 of 2 children treated with ART alone were in complete remission while 1 of 6 patients treated with either vincristine or bleomycin were in complete remission (Gantt 2010). Lastly, both children treated with ART alone were in complete or partial remission as were all 6 children treated with either vincristine or bleomycin (Gantt 2010).

Change in CD4%

Among 28 HIV-infected children diagnosed with KS, the mean CD4% among children only treated with ART was 16% (SD=9.2%), while the mean CD4% among these children after they were treated with both chemotherapy and ART increased to 29.2% (SD=27.1%), yielding a mean difference of CD4% of 13.2 percentage points (1.8-24.7 percentage points) (Vaz 2011). It should be noted that patients had only one month of ART prior to paclitaxel initiation, and baseline CD4% prior to ART initiation was not stated, weakening any causal inference.

Mortality

Cox et al reported the number of patients treated with both chemotherapy and ART and children treated with ART alone who were alive at 12 month follow-up (Cox 2013). They found no significant difference in risk of death among patients treated with both ART and chemotherapy when compared to children treated with ART alone (RR=0.72; 95% CI 0.37-1.43).

Chemotherapy + ART versus chemotherapy alone

KS remission

Compared to chemotherapy alone, the use of ART together with a chemotherapeutic regimen appears to increase the likelihood of KS remission and reduce the risk of death in HIV-infected children diagnosed with KS. Assigning patients with unknown outcomes to the no remission category, we compared children who received a chemotherapeutic regimen (vincristine +/- bleomycin) and ART with children who were treated with chemotherapy alone. Children treated with chemotherapy plus ART combination therapy had a higher unadjusted likelihood of complete KS remission than children treated only with chemotherapy (RR=6.54; 95% CI 1.00-42.86) (Gantt 2010). However, when considering patients with unknown outcomes and assuming no remission, 6 (60.0%) of 10 children treated with chemotherapy alone were in partial or complete KS remission, while 23 (88.5%) of 26 children treated with chemotherapy plus ART were in partial or complete KS remission (RR=1.47; 95% CI 0.87-2.49) (Gantt 2010). When considering only patients with known outcomes, we compared children who

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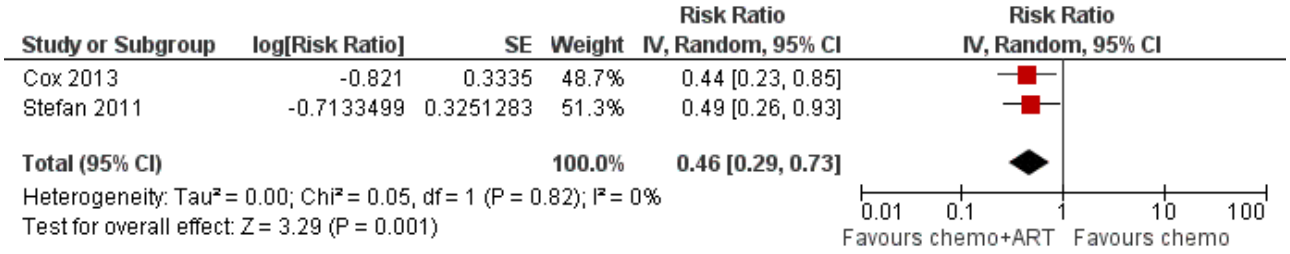
received a chemotherapy regimen (vincristine +/- bleomycin) and ART with children who were treated with chemotherapy alone. There was no difference in the likelihood of complete KS remission between children treated with chemotherapy plus ART and children treated only with chemotherapy (RR=4.25; 95% CI 0.70-25.91), though only 6 children treated with chemotherapy alone had known remission outcomes (Gantt 2010). Similarly, when considering patients with known outcomes, we noted no difference in likelihood of complete or partial KS remission between children treated with chemotherapy plus ART and children treated only with chemotherapy (RR=1.01; 95% CI 0.81-1.27), although again only 6 children treated with chemotherapy alone had known remission outcomes (Gantt 2010).

Mortality

Stefan et al reported the adjusted mortality risk comparing children treated with both chemotherapy and ART and children treated with chemotherapy alone (Stefan 2011) and found a significantly reduced risk among patients treated with both ART and chemotherapy compared to children treated only with chemotherapy (RR=0.49; 95% CI 0.26-0.93). Cox et al reported the number of patients children treated with both chemotherapy and ART and children treated with only chemotherapy (Cox 2013) and also found a significantly lower risk among patients treated with both ART and chemotherapy compared to those on chemotherapy alone (RR=0.44; 95% CI 0.23-0.85), though only 2 children were treated with chemotherapy alone and likely died prior to receiving ART (the likely treatment intention was to give chemotherapy followed by ART to prevent KS-related immune reconstitution inflammatory syndrome). The pooled estimate of mortality risk comparing children treated with both chemotherapy and ART versus children treated with only chemotherapy was RR=0.46 (95% CI 0.29-0.72) (Figure 5), with no heterogeneity (I^2=0%).

Figure 5. Forest plot of comparison: 4 Chemotherapy + ART vs ART, outcome: 4.5 Mortality



Vincristine + ART versus vincristine and bleomycin + ART

KS Remission

The use of ART together with vincristine versus ART combined with vincristine and bleomycin does not appear to be associated with KS remission. Specifically, considering patients with unknown outcomes to not be in remission, we compared children who received vincristine and ART with children who were treated with ART and vincristine and bleomycin. Children treated with vincristine plus ART combination therapy had a similar likelihood of complete KS remission than children treated with ART plus vincristine and bleomycin (RR=0.69; 95% CI 0.33-1.47) (Gantt 2010). Additionally, when also considering patients with unknown outcomes and assuming no remission, 6 of 8 children treated with ART plus vincristine were in partial or complete KS remission compared to 17 of 18 children treated with ART plus vincristine and bleomycin (RR=0.79; 95% CI 0.52-1.20) (Gantt 2010).

When considering only patients with known outcomes, there was no difference in the likelihood of complete KS remission between children treated with ART plus vincristine and children treated with ART plus vincristine and bleomycin (RR=0.92; 95% CI 0.49-1.74), though only 6 children treated with ART and vincristine had known remission outcomes (Gantt 2010). Similarly, when considering patients with known outcomes, we found no difference in likelihood of complete or partial KS remission between children treated with ART plus vincristine and children treated with ART plus vincristine and bleomycin (RR=1.01; 95% CI 0.79-1.29), although again only 6 children treated with ART plus vincristine had known remission outcomes (Gantt 2010).

Combination chemotherapy + ART versus single agent chemotherapy + ART

Mortality

Cox et al reported mortality among children treated with both combination chemotherapy and ART versus children treated with single agent chemotherapy and ART (Cox 2013). Of 36 children treated with combination chemotherapy and ART, 13 died by 12 months of follow up; all 14 children treated with single agent chemotherapy and ART died (RR=0.38; 95% CI 0.24-0.58).

There were not adequate data to perform any subgroup analyses by stage.

DISCUSSION

Although paediatric HIV-associated KS is common in areas of high HIV prevalence, appropriate treatment recommendations in such patients are lacking to guide the practitioner. In a complete review of the literature we found only four cohort studies and no trials that met our inclusion criteria. These four cohorts, while clearly reported, are insufficient for making broad treatment recommendations. Many questions remain as to the most appropriate intervention strategy in paediatric patients with KS. First, an appropriate paediatric staging system must be defined which can be used on a more standard basis. The TIS system as used by Vaz (Vaz 2011) and Cox (Cox 2013) is likely inadequate for paediatric patients while the one utilized by Stefan (Stefan 2011) might be more appropriate. After defining an appropriate staging system, it is also yet to be determined which patients will likely benefit from the addition of chemotherapeutic regimens to ART.

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Considering the potential risks of such treatment, it is unlikely that all patients (especially early-stage patients) will benefit from such therapies. Again, this is yet to be determined based on the available evidence. Finally, for those patients who are likely to benefit from chemotherapy in addition to ART, it remains unclear as to which chemotherapeutic regimen is most effective. The studies reviewed here examine four different regimens, single-agent vincristine, single-agent paclitaxel, bleomycin/vincristine and doxorubicin/bleomycin/vincristine. Sufficient data are lacking to differentiate between these treatment regimens, and no paediatric data are available on the gold standard in adult patients with HIV-associated KS, liposomal doxorubicin. Based on experience in adult KS patients with HIV infection, it is possible that the extent (i.e., stage) of disease is directly correlated to outcome (Martin-Carbonero 2004; Cattelan 2005, Mosam 2012; Bower 2014); those with early stage disease may obtain remission with ART alone while those with advanced disease may benefit from the addition of chemotherapy. Which regimen is optimal for paediatric patients with more advanced disease remains to be fully elucidated. Future studies with more complete data and greater power are needed to answer these questions.

Summary of main results

The use of ART together with a chemotherapeutic regimen versus ART alone appears to increase the likelihood of KS remission and reduce the risk of death in HIV-infected children diagnosed with KS, although data are sparse and not adequately adjusted for staging of disease and comorbidities. Additionally, though data are sparse, the use of ART together with a chemotherapeutic regimen versus chemotherapy alone in some analyses appears to increase the likelihood of KS remission and reduce the risk of death in HIV-infected children diagnosed with KS. Given small sample sizes, we are unable to differentiate whether the use of ART together with vincristine versus ART combined with vincristine and bleomycin is associated with KS remission in paediatric patients with HIV. The use of paclitaxel specifically in paediatric KS patients was examined in one study (Vaz 2011), which reported data that indicate a potential differences in mean CD4% increase between ART alone versus chemotherapy plus ART, though our ability to infer causality is limited due to an absence of baseline CD4% data.

Quality of the evidence

GRADE

In the GRADE system, well-conducted randomised controlled trials (without additional limitations) provide high quality evidence, and observational studies without any special strengths (and without additional limitations) provide low-quality evidence. The quality of evidence provided by a body of literature comprised exclusively of observational studies would thus be graded as "low." In this analysis, we found that the quality of evidence was very low due to small sample sizes and a paucity of pediatric literature. Please see Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3, Summary of findings 4, and Summary of findings 5 for details.

Potential biases in the review process

Biases in the review process were minimised by not limiting the search by language, by performing a comprehensive search of databases and conference proceedings, and by contacting experts in the field for unpublished and ongoing studies. We intended to explore publication bias for the observational studies by using funnel plots, but with only four studies, we were unable to reasonably assess publication bias.

AUTHORS' CONCLUSIONS

Implications for practice

Few studies have adequately studied the impact of chemotherapy and ART for treatment of KS in HIV-infected children. Though some low quality evidence from a few observational studies exists, higher quality evidence from clinical trials in paediatric populations would provide better treatment guidance. The paucity of paediatric studies of KS treatment is potentially an artefact of available treatment options available within low- and middle-income settings.

Implications for research

Randomised controlled trials evaluating the impact of different treatment options for KS in HIV-infected children are needed. Currently, all randomised evidence for KS treatment options is among HIV-infected adult populations.

ACKNOWLEDGEMENTS

We would like to thank Tara Horvath, MA, for performing thorough searches and providing editorial feedback throughout the review process.

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CHARACTERISTICS OF STUDIES

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

Cox 2013

Methods	Retrospective cohort using medical record review
Participants	81 HIV-infected children diagnosed with KS in Malawi and Botswana
Interventions	Chemotherapy with ART versus chemotherapy alone versus ART alone
Outcomes	Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not a randomised study
Allocation concealment	High risk	Allocation not concealed
Blinding All outcomes	High risk	- Not blinded
Incomplete outcome data addressed All outcomes	Low risk	Subjects lost to follow-up unlikely to introduce bias.
Free of selective reporting	Unclear risk	Protocols outlining all outcomes of interest were not available
Free of other bias	High risk	Unadjusted estimates

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Gantt 2010

Methods	Retrospective cohort using medical record review
Participants	73 HIV-infected children diagnosed with KS at Uganda Cancer Institute
Interventions	Chemotherapy (vincristine plus/minus bleomycin) with ART versus chemotherapy alone versus ART alone
Outcomes	Complete (no evidence of residual KS) or partial (any appreciable reduction in size or number of KS lesions) response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not a randomised study
Allocation concealment	High risk	Allocation not concealed
Blinding All outcomes	High risk	Not blinded
Incomplete outcome data addressed All outcomes	High risk	Missing data were not addressed
Free of selective reporting	Unclear risk	Protocols outlining all outcomes of interest were not available
Free of other bias	High risk	Unadjusted estimates

Stefan 2011

Methods	Retrospective cohort
Participants	70 HIV-infected children diagnosed with KS in South African hospitals
Interventions	Chemotherapy plus ART versus chemotherapy alone versus ART alone
Outcomes	Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not a randomised study
Allocation concealment	High risk	Allocation not concealed
Blinding	High risk	Not blinded

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Stefan 2011 *(Continued)*

All outcomes		
Incomplete outcome data addressed All outcomes	Low risk	Subjects lost to follow-up unlikely to introduce bias.
Free of selective reporting	Unclear risk	Protocols outlining all outcomes of interest were not available
Free of other bias	Low risk	Adjusted mortality risk

Vaz 2011

Methods	Retrospective cohort
Participants	28 HIV-infected children diagnosed with KS
Interventions	Chemotherapy (paclitaxel) plus ART (post) vs ART alone--although only one month with ART alone; all patients received paclitaxel
Outcomes	mean CD4%; KS response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not a randomised study
Allocation concealment	High risk	Allocation not concealed
Blinding All outcomes	High risk	Not blinded
Incomplete outcome data addressed All outcomes	Low risk	Complete data; all subjects accounted for
Free of selective reporting	Unclear risk	Protocols outlining all outcomes of interest were not available
Free of other bias	High risk	Unadjusted estimates

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

Study	Reason for exclusion
Ahmed 2012	This is a brief review of treatment options and a description of several cases with no treatment comparisons.
Bunn 2008	This is a brief review of treatment options and case study of 3 KS reports.

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Study	Reason for exclusion
Davidson 2010	Commentary
Niehues 1999	Review

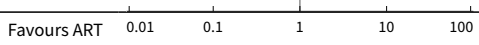
DATA AND ANALYSES

Comparison 1. Chemotherapy + ART vs ART

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete Response to Tx	2	89	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.22, 11.34]
2 Complete/Partial Response to Tx	1	39	Risk Ratio (M-H, Random, 95% CI)	5.75 [1.59, 20.73]
3 Complete Among Known Outcome	1	26	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.48, 1.48]
4 Complete/Partial Among Known Outcome	1	26	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.67, 1.89]
5 Mortality	1	50	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.37, 1.43]
6 Mean CD4% Increase During Chemo	1	48	Mean Difference (IV, Random, 95% CI)	13.2 [1.75, 24.65]

Analysis 1.1. Comparison 1 Chemotherapy + ART vs ART, Outcome 1 Complete Response to Tx.

Study or subgroup	Chemo+ART n/N	ART n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Cox 2013	12/36	7/14		53.86%	0.67[0.33,1.34]
Gantt 2010	17/26	2/13		46.14%	4.25[1.15,15.68]
Total (95% CI)	**62**	**27**		**100%**	**1.57[0.22,11.34]**
Total events: 29 (Chemo+ART), 9 (ART)					
Heterogeneity: Tau^2=1.77; Chi^2=7.19, df=1(P=0.01); I^2=86.1%					
Test for overall effect: Z=0.44(P=0.66)					



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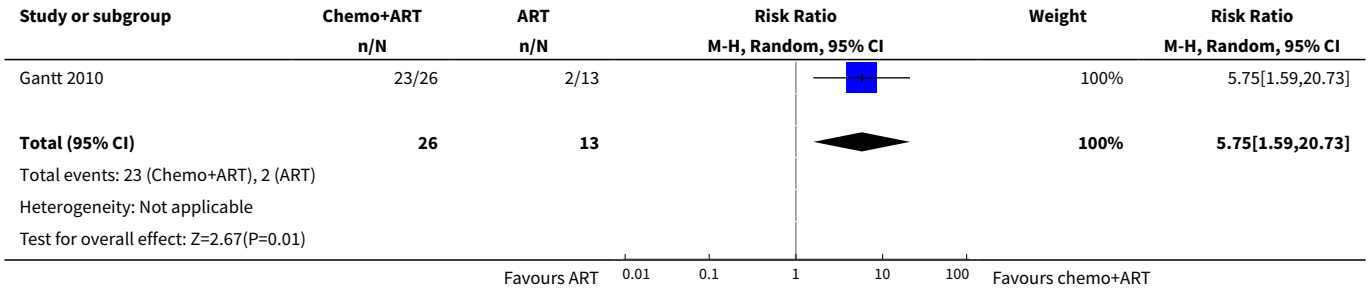
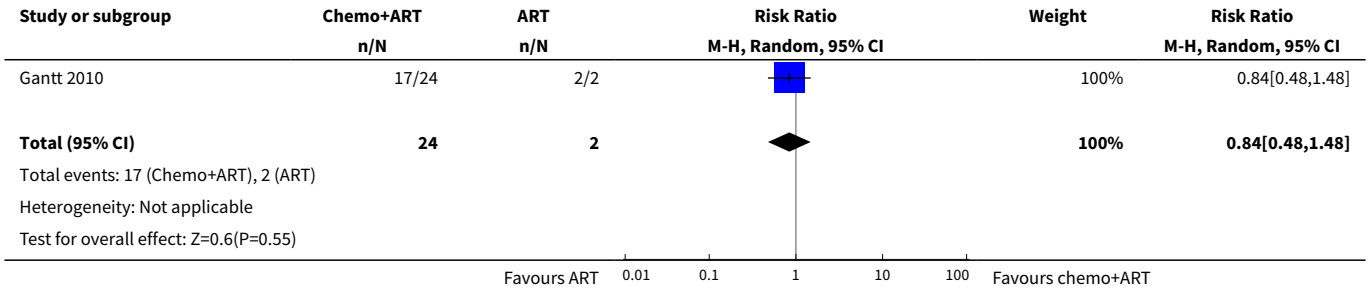
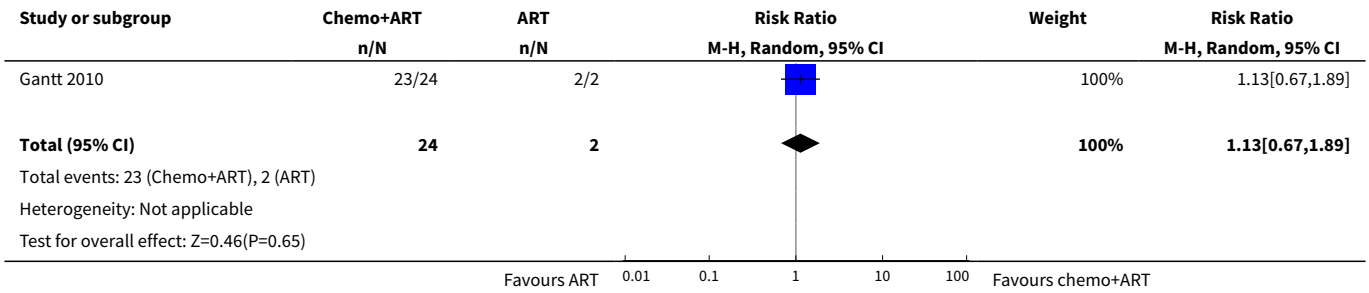
Analysis 1.2. Comparison 1 Chemotherapy + ART vs ART, Outcome 2 Complete/Partial Response to Tx.



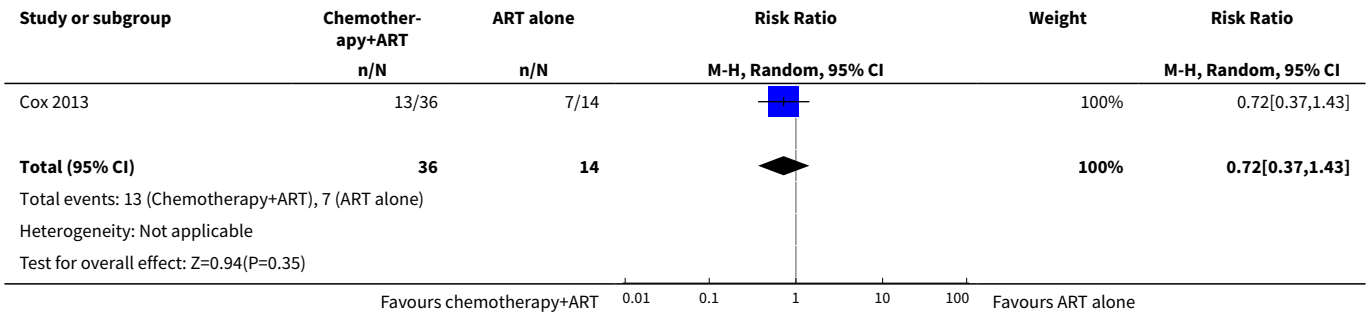
Analysis 1.3. Comparison 1 Chemotherapy + ART vs ART, Outcome 3 Complete Among Known Outcome.



Analysis 1.4. Comparison 1 Chemotherapy + ART vs ART, Outcome 4 Complete/Partial Among Known Outcome.



Analysis 1.5. Comparison 1 Chemotherapy + ART vs ART, Outcome 5 Mortality.



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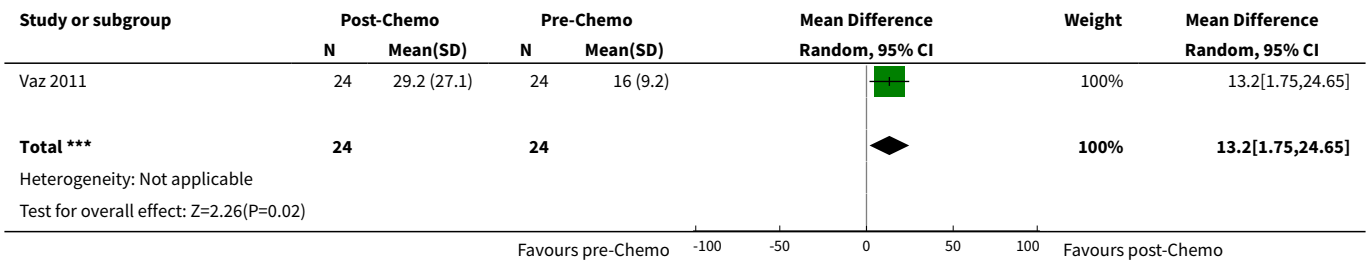
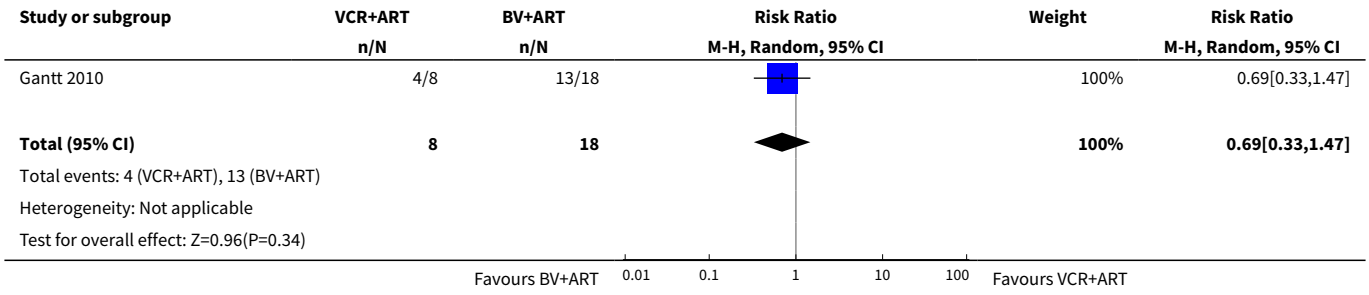
Analysis 1.6. Comparison 1 Chemotherapy + ART vs ART, Outcome 6 Mean CD4% Increase During Chemo.



Comparison 2. Vincristine + ART vs Bleomycin + vincristine + ART

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete: Vincristine+ART vs Bleomycin +vincristine+ART	1	26	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.33, 1.47]
2 Complete/Partial: Vincristine+ART vs Bleomycin+vincristine+ART	1	26	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.52, 1.20]
3 Complete: Vincristine+ART vs Bleomycin +vincristine+ART	1	24	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.49, 1.74]
4 Complete/Partial: Vincristine+ART vs Bleomycin+vincristine+ART	1	24	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.29]

Analysis 2.1. Comparison 2 Vincristine + ART vs Bleomycin + vincristine + ART, Outcome 1 Complete: Vincristine+ART vs Bleomycin+vincristine+ART.



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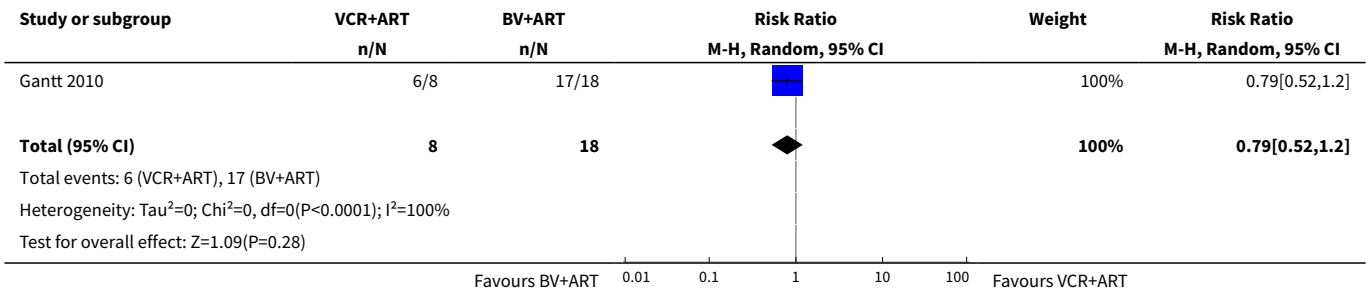
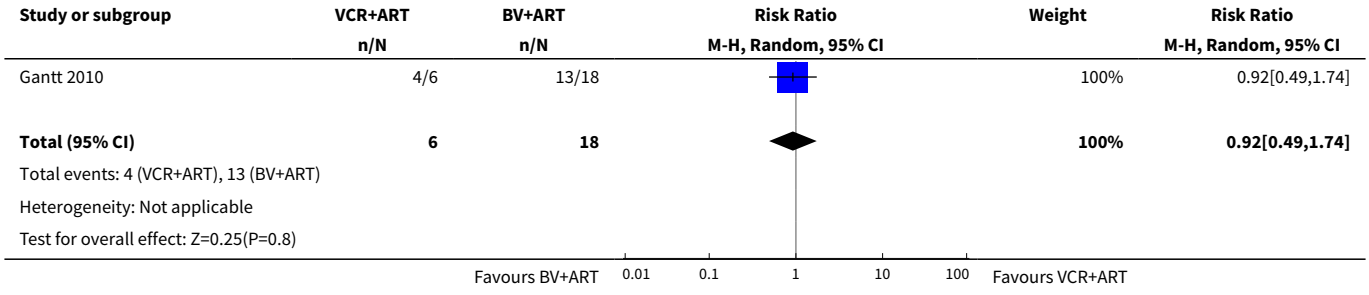
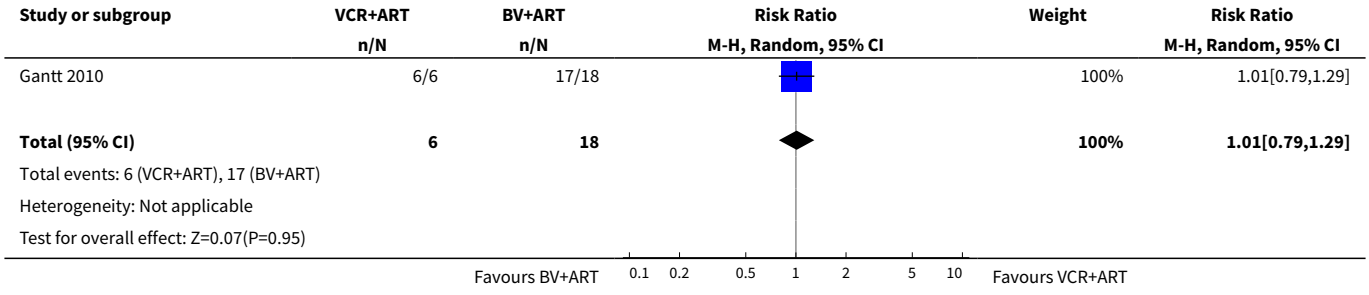
Analysis 2.2. Comparison 2 Vincristine + ART vs Bleomycin + vincristine + ART, Outcome 2 Complete/Partial: Vincristine+ART vs Bleomycin+vincristine+ART.



Analysis 2.3. Comparison 2 Vincristine + ART vs Bleomycin + vincristine + ART, Outcome 3 Complete: Vincristine+ART vs Bleomycin+vincristine+ART.



Analysis 2.4. Comparison 2 Vincristine + ART vs Bleomycin + vincristine + ART, Outcome 4 Complete/Partial: Vincristine+ART vs Bleomycin+vincristine+ART.



Comparison 3. Combination Chemotherapy + ART vs Single Agent Chemotherapy + ART

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	50	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.24, 0.58]

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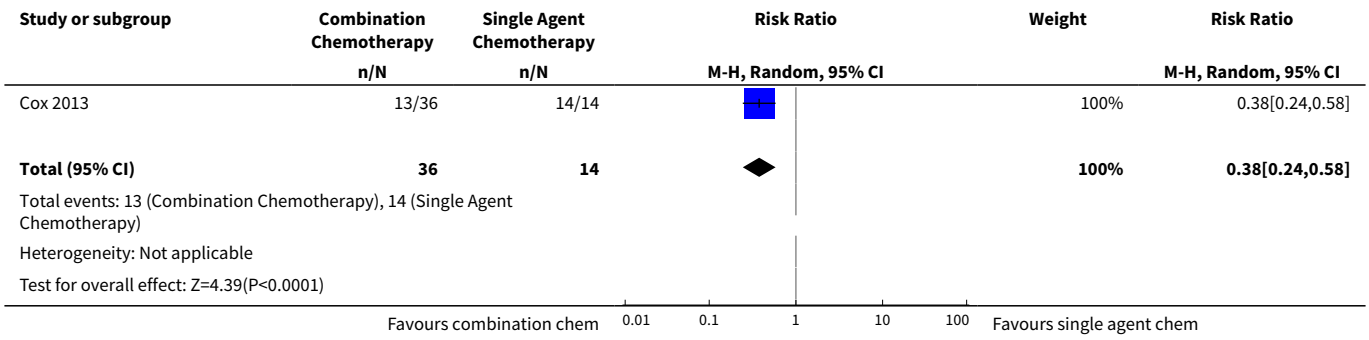
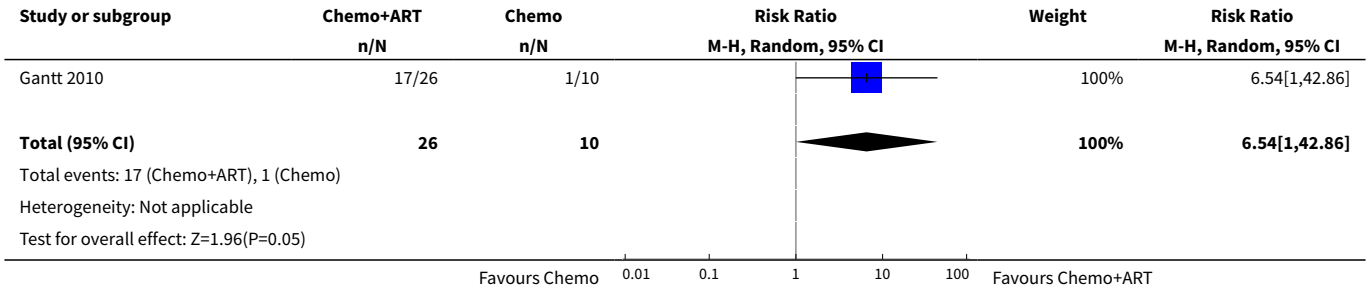
Analysis 3.1. Comparison 3 Combination Chemotherapy + ART vs Single Agent Chemotherapy + ART, Outcome 1 Mortality.



Comparison 4. Chemotherapy + ART vs Chemotherapy Alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete Response to Tx	1	36	Risk Ratio (M-H, Random, 95% CI)	6.54 [1.00, 42.86]
2 Complete/Partial Response to Tx	1	36	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.87, 2.49]
3 Complete Among Known Outcome	1	30	Risk Ratio (M-H, Random, 95% CI)	4.25 [0.70, 25.91]
4 Complete/Partial Among Known Outcome	1	30	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.81, 1.27]
5 Mortality	2		Risk Ratio (Random, 95% CI)	0.46 [0.29, 0.73]

Analysis 4.1. Comparison 4 Chemotherapy + ART vs Chemotherapy Alone, Outcome 1 Complete Response to Tx.



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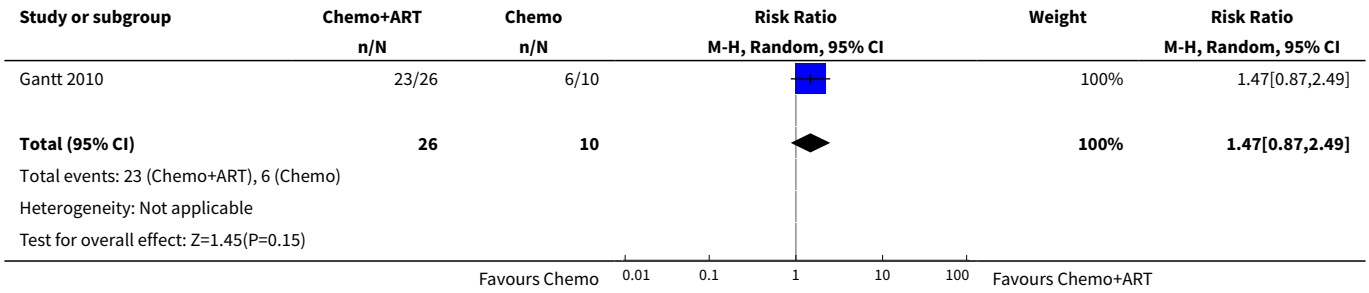
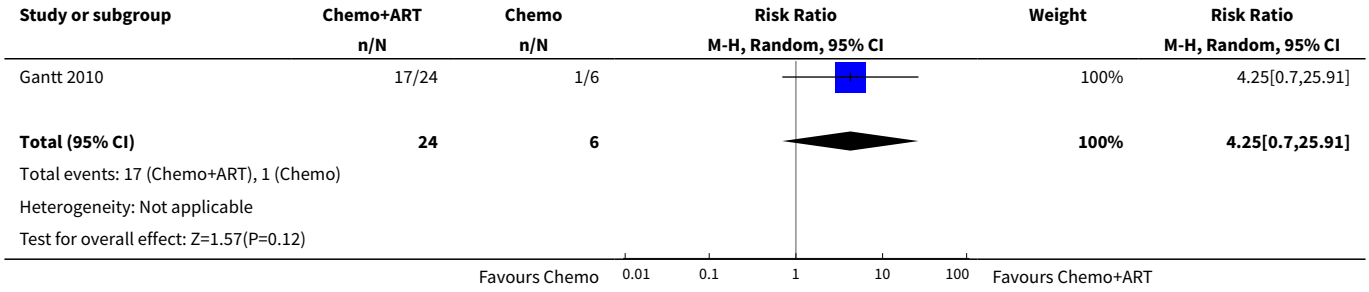
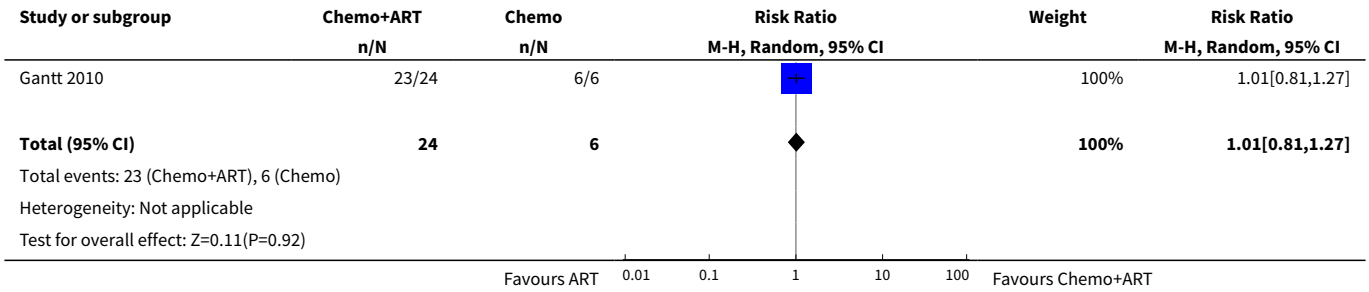
Analysis 4.2. Comparison 4 Chemotherapy + ART vs Chemotherapy Alone, Outcome 2 Complete/Partial Response to Tx.



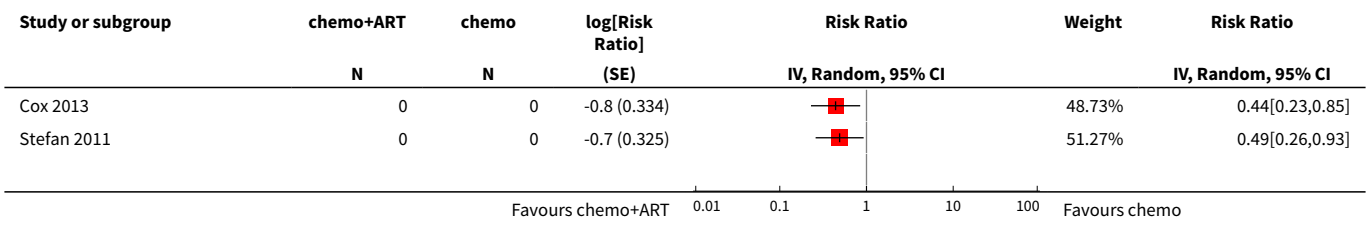
Analysis 4.3. Comparison 4 Chemotherapy + ART vs Chemotherapy Alone, Outcome 3 Complete Among Known Outcome.



Analysis 4.4. Comparison 4 Chemotherapy + ART vs Chemotherapy Alone, Outcome 4 Complete/Partial Among Known Outcome.



Analysis 4.5. Comparison 4 Chemotherapy + ART vs Chemotherapy Alone, Outcome 5 Mortality.



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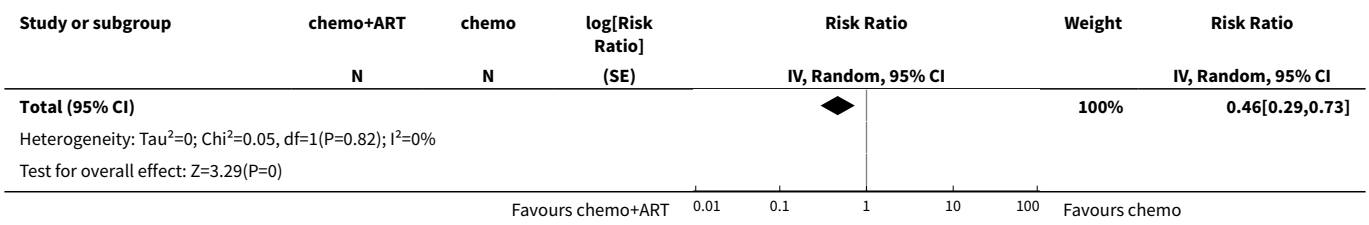
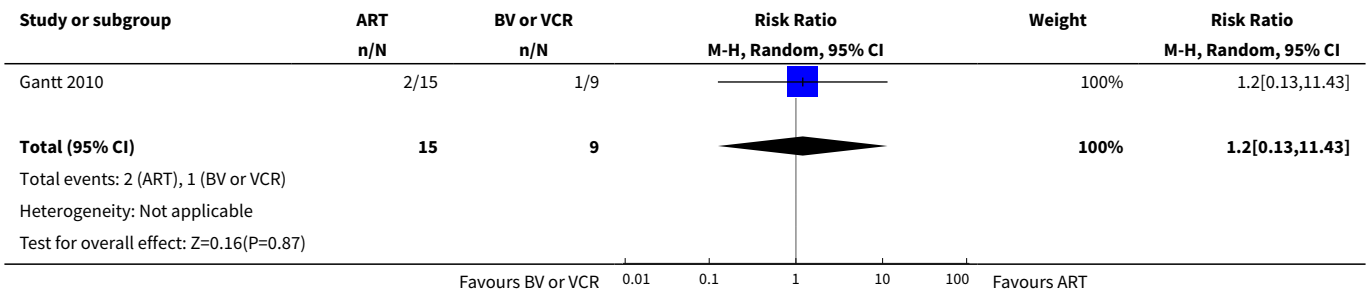


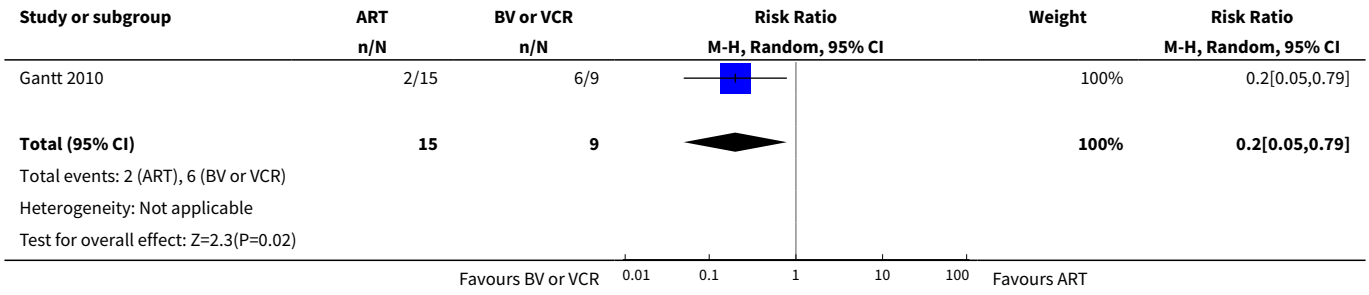
Comparison 5. ART vs Vincristine or Bleomycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete: ART vs Bleomycin or vincristine	1	24	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.13, 11.43]
2 Complete/Partial: ART vs Bleomycin or vincristine	1	24	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.05, 0.79]

Analysis 5.1. Comparison 5 ART vs Vincristine or Bleomycin, Outcome 1 Complete: ART vs Bleomycin or vincristine.



Analysis 5.2. Comparison 5 ART vs Vincristine or Bleomycin, Outcome 2 Complete/Partial: ART vs Bleomycin or vincristine.



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APPENDICES

Appendix 1. Core PubMed search Strategy (modified as needed for use in the other databases)

Core PubMed strategy (modified for use in the other databases)	
#4	#1 AND #2 AND #3
#3	(((HIV Infections[MeSH] OR HIV[MeSH] OR hiv*[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or sexually transmitted diseases, viral[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]))
#2	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])))
#1	(Kaposi sarcoma[MeSH] OR kaposi*[tiab] OR karposi*[tiab] OR Anthracyclines[tw] OR Doxorubicin[tw] OR Epirubicin[tw] OR Daunorubicin[tw] OR Vinca alkaloids[tw] OR Vincristine[tw] OR Vinorelbine[tw] OR Bleomycin[tw] OR Podophyllotoxin[tw] OR Etoposide[tw] OR Teniposide[tw] OR Paclitaxel[tw] OR Docetaxel[tw] OR Thalidomide[tw] OR Lenalidomide[tw] OR Protein kinase inhibitors[tw])

Appendix 2. Newcastle Ottawa Quality Assessment Scale

COHORT STUDIES (Newcastle-Ottawa)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average treated serodiscordant couple in the community

b) somewhat representative of the average treated serodiscordant couple in the community

c) selected group of users (e.g., nurses, volunteers, HIV clinic patients)

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records)

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b) structured interview

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for or matches on disease status when comparing treated and untreated couples

b) study controls for any additional factor (e.g. age or sex)

Outcome

1) Assessment of outcome

a) independent blind assessment

b) record linkage

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest)

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for

b) subjects lost to follow up unlikely to introduce bias - small number lost - > 79% (select an adequate %)

follow up, or description provided of those lost)

c) follow up rate < 20% (select an adequate %) and no description of those lost

d) no statement

NOS - CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort (NB exposure = intervention)

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the study sample from some general population. For example, subjects derived from groups likely to contain exposed people are likely to be representative of exposed individuals, while they are not representative of all people the community.

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3) Ascertainment of Exposure

Allocation of stars as per rating sheet

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4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

A maximum of 4 stars can be allotted in Selection.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

A maximum of 2 stars can be allotted in this category.

OUTCOME

2) Assessment of Outcome

For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation.ï¿½ This may not be adequate for other outcomes where reference to specific tests or measures would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (health records, etc.)

b) Record linkage (e.g. identified through ICD codes on database records)

c) Self-report (i.e. no reference to original health records or documented source to confirm the outcome)

d) No description.

3) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins.

4) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

A maximum of 3 stars can be allotted in this category.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the design and conduct of this review, as well as with manuscript drafting and submission.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

- No external funding, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

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INDEX TERMS

Medical Subject Headings (MeSH)

*HIV-1; AIDS-Related Opportunistic Infections [*drug therapy]; Anti-HIV Agents [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Cohort Studies; Drug Therapy, Combination [methods]; HIV Infections [drug therapy]; Induction Chemotherapy [methods]; Randomized Controlled Trials as Topic; Sarcoma, Kaposi [*drug therapy]

MeSH check words

Child; Humans

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