Annex I. Methodological quality appraisal and Grading of Studies included in the systematic review

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| --- | --- | --- | --- | --- | --- |
| First author: | Setting  | Design  | Quality level of a body of evidence \_GRADE |  | NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE |
| Limitations in the design & implementation | Indirectness Of Evidence | Unexplained heterogeneity  | Imprecision of results | High probability of publication bias: | Grade | Selection  | Comparability  | Outcome |
| Phrill K  ([1](#_ENREF_1)) 2015 | USA | Tennessee Medicaid data linked to vital records | Yes  | no | no | no | no | ++++strong  | Yes based on mother claims \*\* | Good\*\*\* | used a 3-stage process\*\*\* 8//9 |
| Vannappagari, V. 2016([2](#_ENREF_2)) | USA | Follow Up Data Registry | YesExposure classification | yes | no | Yes  | Yes | ++Low | \*\*\* somewhat representative\*secure record\* | Can’t be ruled out effect of other intervention= 0 | \*\*\*Registry & diagnostic base Total =6 |
| Williams et.al.2016 ([3](#_ENREF_3)) | USA | Cohort PHACS SMARTT study | no | YES  | yes | No  | no | +++Strong | 2 drugs were used as HAART \*\* | Potential confounders like BMI cant be ruled out \*\* | Good\*\*\*7/9 |
| Townsend, CL2009([4](#_ENREF_4)) | UK and Ireland  | longitudinal  | No  | no | no | No  | no | ++++Strong  | \*\*\* Some women were Included more than once  | \*\* injecting drug use (ethnic origin,maternal age at delivery & clinical status | \*\* \*\* Registry & diagnostic base 9 |
| Sibiude, J, 2014([5](#_ENREF_5)) | French  | Cohort  | no | no | yes | no | yes | ++++Strong | \*\*\* | \*\* | \*\*\*8/9  |
| Watts DH, 2011([6](#_ENREF_6)) | US, Brazil, the Bahamas  | Cohort  | no | yes | no | no | yes | +++ Moderate  | \*Use of registry\* comparison group  | preconception initiation of ART was notdistinguished from initiation after conception | \*multiple techniques used \*\*Use of standard case definition 5/9 |
| Knapp, KM 2012. ([7](#_ENREF_7)) | US and Europe  | Longitudinal | Yes, Control Group were not clearly stated  | no | yes | no | no | +++ Moderate | \*Adequate Case defn\*Drawn from same community\*ascertainment of exposureonly 41 infantswith efavirenz exposure are included in this analysis. | - comparability not well discussed  | - computerized screening- recorded on clinical casereport forms - panel of clinicians who wereblinded to the mother’s ARV exposure during pregnancy. Deﬁnitiveclassiﬁcation of a congenital anomaly was made byclinician consensus, using the Metropolitan Atlanta CongenitalDefects Program guidelines.Total = 7/9  |
| Bera , 2010([8](#_ENREF_8)) | South Africa | Cohort  | Yes, Classification bias  | no | Yes  | no | no | +++ Moderate  | \*There were switching to NVP after grouping  | \*\*pregnant woman were still on other HAART  | \*\*\* U/S and Visual methods were used to ascertain 6/9 |
| Brogly, 2010([9](#_ENREF_9)) | USA | Cohort  | No  | no | no | no | Yes | ++++strong | \*\* from pro PACTG protocols 219 and 219C data | \*\*\* | \*\*\*Data measured every 3 months 8/9 |
| Zash R, 2016 ([10](#_ENREF_10)) | Botswana  | Cohort  | Yes  | no | Yes(nutrition status)  | no | no | +++ Moderate  | \*\*\*Adequate Case definition | \*Comparison group are on ZDV | \* Adverse pregnancy outcome instead of CA only  |
| Joao, E. C. 2010([11](#_ENREF_11)) | Argentina& Brazil | Cohort  | No | no | Yes(ART Grouping) | Yes | Yes  | ++Week | \*Adequate Case defn\*Drawn from same community\*ascertainment of exposure | \*Classification bias  | \*\*Use of Computer +UltrasoundUse of standard classification5/9 |
| Berard, A.2017([12](#_ENREF_12)) | Canada  | Cohort ( Population based)  | Yes \* inappropriate comparison group  | No  | no | yes | no | +++Moderate  | \*\*population-based and collected many potential confounders. | \* inappropriate comparison group(significant imbalances in most background characteristics) | \*No mention of which congenital classification criteria  |
| Delicio, Adriane M. 2018 ([13](#_ENREF_13)) | Brazil  | Cohort (Retrospective)  | Yes \* inappropriate comparison group | Yes  | Yes Children 0-5 years, Age difference  | no | no | +++Moderate | \*\* Large study Retrospective  | \*\* inappropriate comparison group | \*\* fair 6/9 |
| Van Dyke Dyke, 2016 ([14](#_ENREF_14)) | US, including Puerto Rico | Cohort | Not mentioned  | YeSThe Objective was to study all outcomes | no | no | no | +++Moderate | \*\*Not mentioned however large sample size and sufficient follow-up was used  | \*\* | \*\*6/9 |
| Antiretroviral Pregnancy Registry Committee 2017([15](#_ENREF_15)) | USA | Longitudinal  | Yes \*Passive report inappropriate comparison group | no | Yes  | Yes based on clinician reports | no | ++ week  | Large data \*\* Selection bias  | \*no standard comparison. Usually made with population data  | \*\* based on clinician reports5/9 |
| Mărdărescu M. 2013 ([16](#_ENREF_16)) | Romania  | Cohort  | Yes | no | YesDuration of diseases, BMI  | no | no | +++Moderate | \*\* Smaller sample size, selection bias | \*\*fair  | \*fair 6/9  |
| Zash, R 2019 ([17](#_ENREF_17))  | Botswana  | Cohort  | Yes Follow up study | YesOther ARTs not placebo  | Yes Only Midwives so Clinical Exam | no | no | ++Low  | \*\*\* No matching  | \*\* No matching  | * Only Midwives do the clinical

6/9 |
| Williams 2015 ([18](#_ENREF_18)) | USA  | Cohort Prospective  | No  | No  | Yes  | no | No  | ++++Strong  | \*\*\*\* | \*\* | \*\*Outcome was based on document 8/9 |
| Townsend, CL2006([19](#_ENREF_19)) | UK and Ireland | longitudinal | No  | no | no | No  | no | ++++Strong  | \*\*\* Some women were Included more than once  | \*\* injecting drug use (ethnic origin,maternal age at delivery & clinical status | \*\* \* Registry & diagnostic base 7/9 |
| Prieto LM 2014([20](#_ENREF_20)) | Spain | Cohort  | No  | No  | Yes. Use of Opiates | No  | no | ++++Strong | \*\*\* Women were included at any time | \*\* | \*\*\* European method of classification was used 8/9 |
| Bisio F, 2015 ([21](#_ENREF_21)) | Congo  | Retrospective Cohort  | YesExposure classification | No  | Yes. Other ARTs are also used | Yes | No  | +++Low  | \*\* Women with NVP and other ART also includes | \* | \*\*No clear method of classification was used 5/9 |
| Patel D 2005 ([22](#_ENREF_22)) | Europe  | Cohort  | Yes ascertainment and reportingbias | No  | No  | No  | No  | ++++Strong | \*\*\* ascertainment and reportingbias | \*\* | \*\* Reporting Bias 7/9 |
| Fernandez Ibieta M 2009([23](#_ENREF_23)) | Spain  | Cohort  | YesAnalysis wasX2 or the Fisher test | YesIt compares all ARTs  | No  | No  | YesWide CI and smaller comparison  | ++ Week  | \*\* Women with other ART also includes | * No clear comparison group
 | \*\*No clear method of classification was used 5/9 |
| Hankin CD 2006 ([24](#_ENREF_24)) | UK | Cohort  | YesDocument review  | No  | No  | No  | No  | ++++Strong  | \*\*\* ascertainment and reportingbias | \*\* | \*\* Reporting Bias 7/9 |
| Brogly SB2007([25](#_ENREF_25)) | USA | Cohort  | Yes  | No  | Yesconfounding by maternal viral load and psychoactive drug use | No  | No  | +++Moderate  | \*\*Exposure ascertainmentControlling Confounding  | \*\* | \*\*\* 7/9 |
| Tariq S etal. 2012([26](#_ENREF_26)) | Europe(European Collaborative study)  | Cohort  | Yes\*\*\* HAART for only at least 14 days rather than a month & Presence of other ARTs | Yes  | No  | No  | No  | +++Moderate  | \*\*\* HAART for only at least 14 days rather than a month | \*other HAARTs also include  | \*\* Data for significant 192 participants were missing 6/9  |
| Hill A etal. ([27](#_ENREF_27)) | 6 studies  | Systematic review | Mix up of studiesAnd only 6 studies included  | No  | Yes | Yes  | Yes some are studies by pharmacological companies | ++ week  | \*\* Compared at different exposure status.Only two data bases searched  | \*\* observational studies with out comparison  | * Different outcome ascertainment 5/9
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| Sibiude, J, etal. 2017([28](#_ENREF_28)) | French | Cohort  | No  | No  | Yes other HAARTs | No  | No  | ++++Strong  | \*\*\*\* | \*Yes other HAARTs | \*\*Infected and uninfected children follow-up time 7/9  |

***\*Newcastle-Ottawa Assessment scale;*** *a study can be awarded a maximum number of stars within the selection, comparability and outcome categories. A maximum of 4 stars can be awarded for selection, 2 stars for comparability, and 3stars for outcome, a total score of 9 stars. We qualified studies with scores >5 to be methodologically fit****.***

***+ Grading was done according to the international GRADE group suggestion;****the system classifies quality of evidence (as reflected in confidence in estimates of effects) as high (Grade A ++++), moderate (Grade B++++), or low (Grade C++) according to factors that include the risk of bias, precision of estimates, the consistency of the results, and the directness of the evidence.*

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