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1 **Safety and effectiveness of abacavir for treating infants, children and adolescents**
2 **living with HIV: a systematic review and meta-analysis**

3

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1 **SUMMARY: (299/300 words)**

2 **Background:** Abacavir is a nucleoside reverse-transcriptase inhibitor (NRTI) that is recommended in paediatric
3 HIV care. To address concerns around safety and effectiveness of abacavir use, previously described in adults,
4 we conducted a systematic review and meta-analysis among infants, children and adolescents living with HIV.

5 **Methods:** We searched MEDLINE, Embase and the Cochrane Library bibliographic databases for studies
6 published between Jan 1, 2009 and May 15, 2022. All observational and experimental studies conducted in
7 patients aged 0-19 years living with HIV, with data on abacavir use were eligible. Data were extracted on safety
8 (abacavir-induced hypersensitivity reaction [HSR], treatment discontinuation, adverse events, death), and
9 effectiveness outcomes (virological suppression <400 copies/mL, CD4 counts). Using random effect models, we
10 estimated weighted pooled incidence and relative risks (RR) of outcomes with corresponding 95% confidence
11 intervals (95%CI). PROSPERO registration number: CRD42022309230.

12 **Findings:** Of 1575 records identified, 24 studies were included, with 19 describing safety data and 15 describing
13 effectiveness data. Studies included two randomised controlled trials, one single arm trial, twelve prospective
14 cohorts, seven retrospective cohorts, and two cross-sectional studies. Eighteen studies included ART naïve
15 participants. The risk of bias was considered moderate to high for most studies. Those studies provided data
16 from 24,265 participants, of whom 7236 (30%) received abacavir. Incidence of abacavir HSR (nine studies)
17 ranged from 0% to 8%, with significant between-study heterogeneity ($I^2=85%$, $p<0.001$). Incidence of death
18 (seven studies) varied from 0% to 5% ($I^2=58%$, $p=0.03$), leading to a pooled RR (four studies) of 0.88 [95%CI 0.44-
19 1.74] ($Tau^2=16%$, $p=0.71$). Virologic suppression at 12 months (eight studies) varied from 57% to 78% ($I^2=88%$,
20 $p<0.001$).

21 **Interpretation:** Toxicity events due to abacavir use remain rare, and manageable when it occurs. Despite
22 limited results on effectiveness, this review supports abacavir use as a preferred first-line regimen for infants
23 and children living with HIV.

24 **Funding:** WHO

25

26 **Total words: 3500/3500**

1 **Panel: RESEARCH IN CONTEXT:**

2 **Evidence before this study:**

3 Abacavir is a nucleoside reverse-transcriptase inhibitor that is recommended for use as part of antiretroviral
4 first-line regimen in infants, children and adolescents living with HIV. Previous systematic reviews and meta-
5 analyses in 2015 and 2016 assessed safety and effectiveness associated with abacavir use in this population
6 Overall, few studies were found: 9 and 4 articles on safety and effectiveness respectively, both on ART-naïve and
7 experienced patients. Available findings showed rare toxicity events, such as hypersensitivity reaction, that need
8 to be monitored, especially in the early period of antiretroviral therapy (ART) initiation. Some concerns still
9 remain about abacavir toxicity, with concerning cardiovascular adverse events observed in adults. Abacavir
10 effectiveness (in terms of virologic suppression and CD4 rebound) was similar to other antiretroviral drugs, but
11 this needs further assessment, especially in children and adolescents living with HIV, for whom antiretroviral
12 coverage has to be improved. Since 2015, where universal treatment for all patients living with HIV started to
13 be recommended, and with the implementation of large-scale, paediatric ART program, there is a need to update
14 the state of knowledge on this drug.

15 We searched MEDLINE, Embase and the Cochrane Library from Jan 1, 2009 to May 15, 2022 for all experimental
16 and observational studies in English or French, reporting safety and/or effectiveness outcomes associated with
17 abacavir use in infants, children and adolescents living with HIV. Overall, 24 studies met our eligibility criteria.

18 **Added value of this study:**

19 This systematic review combines both safety and effectiveness outcomes to bring a comprehensive picture of
20 abacavir use in treating infants, children and adolescents living with HIV, focusing on the last decade. Since the
21 last relevant reviews conducted over five years ago, the number of eligible studies has substantially increased,
22 with new findings from two randomised controlled trials and eight prospective cohorts (including two as
23 conference abstracts), updating the review of evidence in this topic. Our results confirmed that abacavir toxicity
24 remains rare and manageable in this population. Abacavir effectiveness compared with other drugs remains
25 unclear with lower effectiveness observed in some cohorts compared with randomised clinical trials. These
26 findings should be interpreted cautiously, as results are highly heterogenous between studies.

27 **Implications of all the available evidence:**

28 Our results confirmed that abacavir can be safely used among infants and children, especially when ART initiation
29 is combined with close monitoring within the first months to prevent abacavir-induced hypersensitivity reaction.
30 However, data remain insufficient for adolescents. Adverse events, not directly attributable to abacavir,
31 remained common in children initiating ART. The recent introduction of new paediatric formulations may reduce
32 the incidence of adverse events and improve effectiveness, which needs to be systematically reported and
33 assessed to strengthen the current level of evidence.

1 INTRODUCTION

2 In 2020, 2.8 million children and adolescents aged 0 to 19 years were living with HIV worldwide, with more
3 than 90% living in sub-Saharan Africa (1). Despite improvements in antiretroviral treatment (ART) accessibility
4 in resource-limited settings over the last 15 years, ART coverage remains suboptimal, and a large gap remains
5 for children compared to adults (54% vs 74% on ART) (1).

6 Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI), that has progressively replaced stavudine (d4T)
7 due to fewer toxicity concerns such as lipodystrophy and metabolic abnormalities (2, 3). Abacavir is also
8 preferred to tenofovir disoproxil fumarate for infants and children, due to concerns about renal toxicity and loss
9 of bone mineral density in this population (4), and lack of paediatric formulation of tenofovir disoproxil fumarate
10 (5). Therefore, in the 2021 WHO HIV consolidated guidelines, abacavir is part of the preferred first-line regimen
11 for children aged ≥ 4 weeks, weighing ≥ 3 kg, coupled with lamivudine and dolutegravir or alternatively ritonavir-
12 boosted lopinavir, while tenofovir disoproxil fumarate is preferred to abacavir in first-line regimens for adults
13 and adolescents ≥ 10 years of age or weighting ≥ 35 kg (6). Abacavir use is however associated with a few toxicity
14 risks that need to be carefully monitored at ART initiation. A rare but concerning adverse event in children and
15 adults is hypersensitivity reaction (HSR), which needs immediate and permanent treatment discontinuation if
16 diagnosed. The presence of HLA-B5701 allele, for which the frequency differs by ethnic group, with lower
17 prevalence found in Black-African populations (7, 8), has been highlighted as strongly associated with the risk of
18 abacavir-induced HSR (9). In adults, abacavir is associated with an increased risk of cardiovascular events (10); a
19 recent international study estimated that there was a 40% increased risk of cardiovascular events in people
20 taking abacavir compared to people not taking abacavir (11). While abacavir has shown antiviral effectiveness
21 in paediatric clinical trials, comparable to other NRTIs in children (12, 13), cohort studies conducted in South
22 Africa highlighted poorer virological responses that need further exploration (14, 15). Previous systematic
23 reviews assessed safety and effectiveness outcomes in children and adolescents receiving abacavir and
24 concluded that abacavir was a viable option for first-line regimens in paediatric HIV, despite few specific studies
25 being available in these populations (16, 17). Large-scale paediatric antiretroviral programmes, with increased
26 access to early diagnosis and life-long therapy, are currently implemented, with the introduction of dolutegravir
27 as the preferred first-line regimen, combined with abacavir among children. In this context, it is important to
28 summarize the latest knowledge on abacavir safety and effectiveness in this population. We conducted a
29 systematic review and meta-analysis to assess the safety and effectiveness profile of abacavir, used in first,
30 second or subsequent lines of treatment, among infants, children and adolescents living with HIV.

31 METHODS

32 **Search strategy and selection criteria:**

1 To inform 2021 WHO paediatric ART recommendations, we conducted a systematic review and meta-analysis,
2 for which the protocol is published in PROSPERO (CRD42022309230). Results were reported following the
3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All observational and
4 experimental studies conducted in infants (0-1 year), children (aged 1-10 years) and adolescents (aged 10-19
5 years) living with HIV, with data on safety and/or effectiveness of abacavir-based antiretroviral therapy,
6 published either in English or French between January 1st 2009 and October 1st 2020 were considered for
7 inclusion, an updated search strategy was then conducted for incorporating studies published between October
8 1st 2020 and May 15th 2022. Studies could be non-randomised or non-comparative, and the study population
9 could be treatment-naïve or experienced, as long as they received abacavir in combination with other
10 antiretroviral (ARV) therapies. Case studies, studies reporting on an adult population that included patients aged
11 ≥ 18 years only, and studies assessing the effect of maternal exposure of ARVs were not part of the inclusion
12 criteria.

13 We searched studies published in MEDLINE (via the Web of Science), Embase and the Cochrane Library
14 (CENTRAL) using both free-text terms and index terms, combining terms for HIV, abacavir, children and
15 adolescents (Tables S1a and S1b). Grey literature sources were also searched, by hand screening reference lists
16 of systematic reviews, recent international guidelines on HIV treatment and any other relevant studies identified
17 previously, as well as clinical trial registries for studies updated between January 2018 and October 2020 and
18 targeted conference abstract books published between January 2018 and October 2020 (Table S2). Study
19 authors were contacted when further clarifications were needed.

20 Titles and abstracts and then full texts were independently screened by two reviewers (JJ and VL), with the
21 technical support of the Rayyan web app (18). Main reasons for exclusion during the full paper review stage
22 were documented. Discordance was resolved by discussions with the project team. This review constitutes an
23 update of a previous review published in 2016 (16) regarding safety outcomes, and included new results on
24 effectiveness outcomes.

25 **Data analysis:**

26 We extracted data related to study identifier, study design, study period, setting, population characteristics
27 (including sex and age groups), ART treatment (including comparative groups and ART-experience), and safety
28 and effectiveness outcomes using a piloted data extraction spreadsheet. Data extraction was done unblinded by
29 a single reviewer (JJ), and checked and validated independently by a second reviewer (VL). The following safety
30 outcomes were reported: hypersensitivity reaction (HSR); death; grade 3/4 adverse events; treatment
31 discontinuation; any other morbidities and serious adverse events (defined as any adverse event or reaction that
32 is life-threatening, requires hospitalisation, results in persistent or significant disability or incapacity, or another
33 important medical condition). Effectiveness outcomes extracted were HIV viral load, expressed as virological

1 suppression using a threshold of 400 copies/mL or 50 copies/mL; and CD4 counts, expressed in cell counts or
2 percentage. Both measures were commonly reported at 6 and 12 months after ART initiation.

3 The quality of scientific evidence and the overall risk of bias in the included studies were assessed using the
4 Cochrane Risk of Bias tool 2.0 (Version 2) for randomised controlled trials (RCTs), the National Institute of Health
5 quality assessment tool for non-randomised interventional studies and the Clinical Advances through Research
6 and Information Translation (CLARITY) tool for observational studies.

7 Safety and effectiveness outcomes according to abacavir exposure were first described within a narrative
8 synthesis. Pooled incidences of safety and effectiveness outcomes were then estimated with their 95%
9 confidence intervals (95%CI) using a meta-analysis with a random-effect model and building forest plots.
10 Heterogeneity between studies was assessed by quantifying the inconsistency between incidence rate estimates
11 with the Q, χ^2 , and the I^2 statistics, calculated with MetaXL software (EpiGear International Pty, Sunrise Beach,
12 QL, Australia). Only analyses with $I^2 \leq 90\%$ are displayed using forest plots. Relative risk of safety and effectiveness
13 outcomes between the abacavir-containing regimen group (intervention group) and the non-abacavir-
14 containing regimen group (control group) were summarised by risk ratio (RR) with their 95%CI, using
15 DerSimonian and Laird random-effects models and building forest plots. Heterogeneity between risk ratio was
16 assessed using the tau² statistic, calculated with Review Manager 5.4 (Cochrane Collaboration, Copenhagen,
17 Denmark).

18 **Role of the funding source:**

19 This work was supported by the WHO. The opinions expressed here in interpretation and manuscript writing
20 contributions are those of the authors and do not necessarily reflect the views of the funder.

21 **RESULTS**

22 Among the 1777 records identified through database searching, 1475 remained after removing duplicates, of
23 which 1421 were excluded based on title and abstract screening. Among the 54 records screened based on full-
24 text, 33 were excluded. Four records were identified through grey literature searches, with one duplicate from
25 the database searching strategy, leading to a total of 24 studies included (Figure 1).

26 Data from 24,265 participants were included, of whom 7,236 (30%) received abacavir. Nineteen (79%) studies
27 included safety-related data and 15 (62%) included effectiveness-related data. Two studies (8%) were
28 comparative RCTs (13, 19) and one (4%) was a single arm phase 2 trial with abacavir being used as backbone
29 (20). Twelve studies (50%) were prospective cohorts (15, 21-31), including one being a cohort nested in a RCT
30 (21). Seven were retrospective cohorts (29%) (14, 32-37) and two (8%) were cross-sectional surveys (38, 39).
31 These studies were conducted in various settings: nine in Southern Africa (37%) (Zambia, South Africa,
32 Zimbabwe), six in Eastern Africa (25%) (Ethiopia, Uganda, Malawi), two in Western Africa (8%) (Ghana, Nigeria),

1 three in South Asia (12%) (India), three in Europe (12%) and three in North America (12%). Four studies were
2 multiregional (17%) (13, 20, 27, 28). The study period ranged from 1998 to 2019, and eleven studies (46%)
3 started in 2010 or later. Eighteen studies (75%) were conducted among ART naïve participants. Follow-up varied
4 between 48 weeks up to more than 5 years. Median age ranged from 2 months up to 17 years at inclusion.
5 Respectively seven (29%) and nine studies (37%) included infants less than 12 months and adolescents aged 10
6 years or older at baseline (Table 1).

7 The two comparative RCTs were classified as low risk of bias while the single-arm trial was classified as moderate
8 risk. Of the 21 observational studies, one (5%) was classified as low risk of bias, eight (40%) as moderate risk or
9 unclear risk of bias. Twelve (60%) were classified as high risk, the main reasons being the retrospective study
10 design, which reduces confidence in exposure and outcome assessments (Figure S3).

11 Regarding the safety outcomes (Table 2), abacavir hypersensitivity reaction was reported in nine studies (39%)
12 (one RCT, one single-arm trial and seven prospective cohorts) (13, 20, 22, 23, 27-31), with an incidence ranging
13 from 0% to 8% and a significant between-study heterogeneity ($I^2=85%$, $p<0.001$) (Figure 2). The RCT by Mulenga
14 et al. compared HSR by drug regimen (13), and reported an incidence of 1%, 3% and 0.6% for the abacavir,
15 stavudine and zidovudine groups, respectively, with no statistical difference between groups ($p=0.21$). All these
16 children on abacavir with grade 1 to 4 HSR stopped the drug without any further adverse effects notified. In the
17 single-arm trial by Fortuny et al. (20), among the nine HSR notified, two were related to fosamprenavir/ritonavir
18 according to the investigators, two occurred after abacavir was stopped and were related to cotrimoxazole, and
19 no death was reported. In the prospective cohort by Chakravarty et al.(31), among the 101 children started on
20 abacavir during the study period, 8 [7.9% (95%CI 3.5-15.0%)] children developed clinically diagnosed abacavir
21 HSR, and symptoms resolved after stopping abacavir in all children. Among them, all those with concomitant
22 illness (4/8) were HLA-B05701 negative, and two children carried the HLA-B05701 allele. The six other studies
23 reported low rates of HSR, below 2%.

24 All-cause treatment discontinuation was reported in one RCT (20) and four prospective cohorts (22, 23, 27, 28),
25 with an incidence ranging from 1% to 14% and significant between-study heterogeneity ($I^2=97%$, $p<0.001$).

26 Five studies described adverse events overall, such as skin rash, pneumonia, or gastrointestinal symptoms (13,
27 20, 27, 28, 35). Two studies specifically reported grade 3/4 adverse events (13, 20). In the RCT by Mulenga et al.
28 (13), 917 grade 2-4 clinical or grade 3/4 laboratory adverse events (835 clinical; 40 laboratory) occurred in 104
29 (67%) children on stavudine, 103 (65%) on zidovudine, and 105 (64%) on abacavir ($p=0.63$; zidovudine vs
30 stavudine: hazard ratio [HR] 0.99 [95%CI 0.75-1.29]; abacavir vs stavudine: HR 0.88 [0.67-1.15]). Although
31 frequently reported, the risk of grade 3 or 4 adverse events was not significantly higher for abacavir compared
32 to other drugs. Two prospective studies by Patel et al. explored cardiovascular risks among children (24) and
33 adolescents (25) and found no effects of abacavir use (incident cardiomyopathy: adjusted odds ratio, abacavir

1 use Yes vs No 0.7 [0.3, 1.5]). Other adverse events described were lipodystrophy (n=5, 4.7%) (19), mitochondrial
2 toxicity (13, 34), change in insulin resistance (6%) (21), and growth outcomes (19, 32) (Table 2).
3 Mortality rate was reported in seven studies (13, 14, 19, 27, 29, 32, 35). The incidence of death on abacavir
4 varied from 0% to 5%, with significant between-study heterogeneity ($I^2=58%$, $p=0.03$). Four studies compared
5 the mortality rate according to ART regimen, with a homogeneous pooled estimate of the relative risk of death
6 for children on abacavir compared to other drugs (RR=0.88 [95%CI: 0.44-1.74], $\tau^2= 16%$, test for the overall
7 effect $p=0.71$) (Figure 3).

8 Regarding effectiveness outcomes (Tables S2a and S2b), five studies reported viral load suppression at a
9 threshold of 400 copies/mL at 6 months (14, 15, 23, 28, 32), and eight studies at 12 months or 48 weeks (13-15,
10 20, 21, 23, 28, 32). Viral suppression varied from 50% to 70% at 6 months and from 57% to 78% at 12 months,
11 with significant heterogeneity between studies ($I^2 =92%$ and $88%$ respectively, $p< 0.001$). In a large prospective
12 cohort in South Africa reported by Technau et al. in 2014 (15), a significantly lower viral suppression rate was
13 reported in the abacavir group at 6 and 12 months compared to the stavudine group, whatever the backbone
14 used (efavirenz [RR at 12 months: 0.56; 95%CI: 0.36-0.86] or ritonavir-boosted lopinavir [RR at 12 months: 0.52;
15 95%CI: 0.39-0.69]) (Table 3a). Similar results were reported from a retrospective cohort in 2013 by the same
16 author (14). On the contrary, viral suppression rates were similar between the abacavir and the stavudine groups
17 at 6 and 12 months in the retrospective case-control study of Cassim et al. (32).

18 Four studies reported CD4 data related to abacavir treatment (19, 29, 32, 36), with three being comparative. In
19 Strehlau et al. (19) and Cassim et al. (32), the CD4 percentages were similar between the abacavir and the
20 stavudine group over time (Table 3b). In Mega et al. (36) CD4+ cell count gain per 6 months was significantly
21 higher in the zidovudine group compared to the abacavir group ($p=0.004$).

22 **DISCUSSION**

23 This systematic review and meta-analysis showed that overall, abacavir can be used safely and effectively for
24 infants and children, while specific data on adolescents remain insufficient, which aligns with the 2021 WHO
25 paediatric ART recommendations. The major feared abacavir-related toxicity event, HSR, was reported in less
26 than 2% of participants for most studies. Other adverse events reported were not specifically associated with
27 abacavir use. There was no difference in risk of mortality for participants receiving abacavir compared to those
28 on other ARV drugs. Except in two South-African cohort studies that highlighted a lower viral suppression rate
29 in the abacavir group (14, 15), CD4 counts and viral load at 6 or 12 months after ART initiation were not different
30 between abacavir and stavudine-based regimen. One study showed higher CD4 count gain at 6 months for
31 zidovudine-based regimens compared to abacavir-based regimens (36). Most outcomes were reported
32 heterogeneously between studies, and except for two randomised trials, studies were considered of moderate
33 to high risk of bias. Data interpretation therefore needs to be made cautiously.

1 HSR is the main toxicity event associated with abacavir use. In our review, no HSR cases led to worse adverse
2 events such as death, and symptoms rapidly resolved after abacavir-treatment discontinuation. The incidence
3 of HSR ranged from 0% to 2% in seven of the nine studies included, all being resolved with abacavir cessation,
4 and the other two studies reported an incidence of 8% (20, 31). The first was a prospective cohort conducted
5 between 2013 and 2014 in India, with the specific aim to observe the incidence of clinically diagnosed HSR (31).
6 This study was at high risk of bias due to its non-specific definition of the outcome, which could have led to
7 overestimating the incidence of abacavir-induced HSR. The second study was a multiregional open-label RCT
8 conducted between 2004 and 2010, evaluating the pharmacokinetics and safety of fosamprenavir-based
9 regimens, with abacavir used as a backbone (20). No data on HLA-B05701 screening before ART initiation were
10 available in this study, which might partly explain the high rate of abacavir-induced HSR reported. The screening
11 of HLA-B5701 is now recommended before initiating abacavir-based regimens in all people living with HIV to
12 prevent the onset of HSR. The low HSR incidence reported in other studies might therefore be explained by the
13 common use of HLA-B5701 screening before ART initiation. This screening might be more easily implemented in
14 HIV clinics participating in research programs, explaining why the incidence of HSR reported in scientific
15 publications is low. However, the test for HLA-B5701 is costly and not done systematically in HIV-clinics from
16 resource-limited settings that need to be further supported to detect and reduce abacavir-induced HSR. While
17 testing for HLA-B5701 is standard-of-care in high-income settings, gaps in terms of cost and access remain in
18 resource-limited settings, that could be addressed by developing rapid and inexpensive tests (40, 41).

19 Two studies conducted by Patel et al. (24, 25) specifically assessed the risk of cardiovascular diseases in children
20 and adolescents living with HIV, and did not find an increased risk associated with abacavir use. However, in the
21 study conducted in adolescents, the duration of ABC use was less than a year in median, which may be a too
22 short exposure to observe cardiovascular adverse events. In contrast, several observational studies conducted
23 in adults (10, 42) highlighted higher risk of cardiovascular diseases for those using abacavir, while a pooled
24 analysis of findings in adults enrolled in clinical trials showed no different risk associated with abacavir use (43).
25 Further studies assessing the causes of cardiovascular diseases of children and adolescents on long-term ART
26 regimen are needed to better prevent those co-morbidities, especially in resource-limited settings where most
27 of this population live and where monitoring tools are lacking (44).

28 We found few eligible studies published between 2009 and 2022, with a lack of homogeneous, standardised
29 data collection across studies. Few studies specifically addressed abacavir safety and effectiveness among
30 adolescents, which does not allow abacavir to be recommended for this age group. Few participants were
31 initiated on ART during infancy, and two of the seven articles focusing on infants were conference abstracts.
32 Most comparative studies were comparing abacavir use with stavudine use, which is not recommended
33 anymore for children as a first-line regimen. No studies were found describing abacavir safety and

1 effectiveness while combined with more recently introduced ARVs such as integrase strand transfer inhibitors,
2 while dolutegravir-based regimen could lead to lower levels of viral suppression in children with predicted
3 abacavir resistance as found in a recent study conducted in Kenya (45). Questions remain on drug susceptibility
4 for abacavir when used as second-line ART. Only the CHAPAS-3 trial (13) identified a lower susceptibility to
5 abacavir second-line for those taking first-line zidovudine among virologically suppressed children, which could
6 affect effectiveness. No data were found on children getting second-line ART due to treatment failure. Further
7 research reporting results by ART drug rather than regimen are therefore needed to better address such
8 critical questions like the effectiveness of NRTI backbone while combined with integrase strand transfer
9 inhibitors, and the effectiveness of ART drug while used as second-line ART, especially in a context of
10 treatment failure. Similarly, growth outcomes such as weight-for-age and height-for-age evolution might be
11 significantly associated with the type of ART drug, however few studies describe this association, with
12 conflicting results while comparing protease-inhibitor-based versus non-nucleoside reverse transcriptase
13 inhibitors-based regimen (46). We found only two studies comparing these outcomes according to ABC use in
14 our review, with no differences highlighted between groups (19, 32). Furthermore, all studies, including RCTs,
15 were unblinded on the ARV regimen used, which might have impacted the reporting of minor or moderate
16 adverse events but not severe ones. Mortality was not reported systematically – only one study specified that
17 no deaths occurred (19) – which might suggest an overestimation of our pooled mortality rate. In addition, the
18 non-comparative or retrospective study design used in most studies meant that most were rated as moderate
19 or high risk of bias overall, which limits our interpretation and conclusions. Finally, publication bias was
20 reduced by the addition of grey literature sources in our search strategy, and by discussing and sharing
21 experiences with our paediatric HIV research network. Although our search strategy focused on articles
22 published from January 2009 onwards, we believe this cut-off was appropriate given that abacavir was first
23 approved for use in paediatric patients in the US in December 2008 (47), and included in WHO paediatric ART
24 recommendations in 2010 (48). Therefore, our review includes all studies that implemented abacavir-based
25 regimens in line with official recommendations for dosing and clinical management.

26

27 Nevertheless, this comprehensive systematic review summarizes the most recent evidence on safety and
28 effectiveness of abacavir-based regimens among infants, children and adolescents and aligns with conclusions
29 made in previous systematic reviews (16, 17). Systematic reviews conducted in adults highlighted more serious
30 toxicity events such as cardiovascular diseases (10), however, our findings support the recommendation to use
31 abacavir as the preferred first-line regimen for infants and children. Specific data on adolescents are insufficient
32 to provide recommendations for this age group. To conduct individual patient data meta-analyses could help
33 further assess the effectiveness of abacavir as NRTI backbone, especially when combined with newly introduced

1 integrase strand transfer inhibitors. To conclude, this work advocates for further research studies to be
2 conducted among infants, children and adolescents to monitor and assess ART toxicity and safety, to further
3 improve ART tolerance, adherence and finally the quality of life of infants, children and adolescents living with
4 HIV.

5

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1 **Contributors**

2 JJ and VL conducted the search strategy and data extraction, with support and discussions with LSL and MHD.
3 The data analyses were collectively run by JJ, LSL, MHD and VL. JJ wrote the first draft of the manuscript with
4 further input from all co-authors. All authors contributed to the protocol development, had full access to the
5 data, reviewed and edited the manuscript. The corresponding author, JJ, had final responsibility for the
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7 **Declaration of interests**

8 CT received consultancy fees from the World Health Organisation and the International AIDS Society, and JOR
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12 **Data sharing**

13 All data used for the study has been included in the manuscript and supplementary material.

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Table 1: Characteristics of the 24 studies included in the systematic review on abacavir safety and effectiveness, 2009-2020

First Author, Year of publication - Setting	Study period	Study design - Length of follow-up	Total (On ABC)	ART regimen, comparison group	Treatment experience and duration	Median or Mean age at baseline	Sex (Male %)
Mulenga, 2016 - Zambia & Uganda ¹³	2010-2011	Randomized Clinical Trial (RCT) Open-label, parallel-group, 3-arms randomised trial (CHAPAS-3) - 96 wks	478 (164)	d4T, n=156 ZDV, n=158	ART naïve=76% ART exp=on d4T for > 2 yrs with VL less than 50 copies per mL	ART naïve: median 2-6 yrs [IQR 1-6-4-0] ART-exp: median 6-2 yrs [IQR 5-5-7-2]	ART naïve: 49% ART-exp: 52%
Dirajlal-Fargo, 2017 - Uganda ²¹	2010-2011	Sub-study of CHAPAS-3, cohort nested in RCT - 48 wks	118 (41)	d4T, n=42 ZDV, n=35	ART naïve	Median 2.8 yrs (1.7-4.3)	49%
Strehlau, 2018 - South Africa ²⁰	2010-2013	RCT, unblinded, substitution of ABC for d4T in children who were virally suppressed without lipodystrophy - 56 wks	213 (107)	d4T vs ABC substituted for stavudine	ART exp Duration on ART (Mean ± SD): ABC: 3.5y ± 0.26 d4T: 3.3y ± 0.8	Mean ± SD ABC: 4.2y ± 1.0 d4T: 4.2y ± 0.9	47%
Fortuny, 2014 - North America, Europe and South Africa ¹⁹	2004-2010	Phase II, open-label, multicenter single-arm trial - 48 wks	109 (109)	Fosamprenavir with or without ritonavir (ABC used as backbone, no comparison according to ABC)	ART naïve=38% ART exp/PI-naïve=26% PI-exp=37%	Median 9 (2,18) yrs	47%
Technau, 2014 - South Africa ¹⁵	1998-2013	Prospective cohort - Up to 15 mo	9543 (1536)	d4T vs ABC, based on EFV or LPV/r	ART naïve	Median (IQR) in mo: between 7 (4-18) (LPV/r based) and 96 (63-129) (EFV based)	50%
Fortuin-De Smidt, 2017 - South Africa ²²	2004-2014	Prospective cohort - median 41 mo (IQR 14-72)	3579 (1043)	Most common: 3TC-d4T + either EFV in children >3 yrs (61%) or LPV/r in children <3 yrs (52%)	ART naïve	Median (IQR) in mo: 44 (13-89)	50%
De Waal, CROI 2020, poster 845. - South Africa ²³	2006-2017	Prospective cohort - Median (mo): ABC: 15.0 (IQR 4.2-36.2) ZDV: 10.6 (IQR 2.5-25.6)	1275 (931)	ZDV	ART naïve	Median (IQR) in days: ABC: 67 (48-80) ZDV: 32 (6-66)	44%
Patel, 2012 - United States ²⁴	1993-2007	Prospective cohort - median 5.5 yrs	3035 (789)	ABC use Yes vs No	ART naïve=520 (17%) ART exp=2515 (83%)	44% ≤ 5 yrs of age	49%
Patel, 2014 - United States ²⁵	2007-2009	Prospective cohort - 4 yrs	165 (Current 46, Ever 79)	ABC use Yes vs No	ART exp Duration on ART (median, IQR): Overall: 11.0y (7.7, 12.5) ABC use: 0.0y (0.0, 3.3)	Median (IQR) in years: 16.7 (15.9, 17.8)	49%
Tadesse, 2019 - Ethiopia ²⁶	2017-2019	Prospective cohort - 48 wks	111 (37)	3TC-EFV + either ZDV (14%), ABC (33%) or TDF (53%)	ART naïve	Median (IQR) in years: 9 (5-12)	47%
Nahirya-Ntege, 2011 - Uganda, Zimbabwe ²⁷	2007-2010	Prospective cohort (nested in the ARROW RCT) - 3.5- 5 yrs	1150 (1150)	No comparison. Combination was ABC+3TV + EFV or NVP, ± NVP	ART naïve	From 3 mo to 17 yrs (median 6 yrs)	50%
Crichton, CROI 2020, poster 844	2000-2016	Prospective cohort	139 (139)	No comparison. Most common combination were ABC+3TC+LPV/r	ART naïve	Median (IQR) in days: 62 (35-78)	40%

- Europe (11 countries) ²⁸		- Median yrs (IQR)=4.6 (1.5-9.7), outcomes at 12 mo of follow-up		(39%), ABC+3tc+ZDV+NVP (32%), ABC+3TC+NVP (14%)			
Pareek, 2019 - India ²⁹	2015-2016	Prospective cohort - 12 mo	48 (48)	No comparison. ABC+3TC+ NVP (n=32) or ABC+3TC+EFV (n=16).	ART naïve	Mean (SD) in years: 9.8 (3.4)	75%
Manghani, 2018 - India ³⁰	2013-2014	Prospective cohort - Up to 12 mo	100 (100)	No comparison.	ART naïve (n=90) or exp (n=10). Duration on ART, median (range) in days: ART-naïve: 7 (3 -15) ART exp: 88 (16 - 774)	Median (range) in years: 11 (2 to 18y)	61%
Chakravarty, 2016 - India ³¹	2013-2014	Prospective cohort - Up to 12 mo	101 (101)	No comparison.	ART naïve (n=27) or exp (n=73). Duration on ART, median (IQR) in months: 12.5 (0-24.0)	Mean (SD) in years: 5.8 (3.5)	70%
Cassim, 2017 - South Africa ³²	2005-2013	Retrospective case-control study - 12 mo	171 (57)	d4T	ART naïve	Median (IQR) in months: 3.11 (1.98-6.05)	43%
Technau, 2013 - South Africa ³⁴	2004-2011	Retrospective cohort - 12 mo	2036 (402)	d4T/3TC vs ABC/3TC, in combination with either EFV or LPV/r	ART naïve	Median (IQR) in months: LPV/r based: 10 (4-20), EFV based: 86 (60-119)	50%
Frangé, 2011 - France ³³	2000-2009	Retrospective cohort - Median (IQR) follow-up during LPV/r treatment: 36 mo (18 -72)	43 (19)	LPV/r based with the following backbone: 3TC (84%), ZDV (60%), d4T (12%), ABC (44%)	ART naïve	Median (IQR) in years: 4.8 (1.8 - 8.0)	60%
Langs-Barlow, 2013 - Ghana ³⁴	2004-2011	Retrospective cohort - No information	403 (44)	Most common HAART regimen use was ZDV-3TC, and either EFV or NVP	both ART naïve (72, 8%) and ART exp (331, 82%)	Mean (SD) in months: ART Naïve: 108.1 (41.4) ART exp: 97.3 (40.7)	ART Naïve: 44% ART exp: 52%
Mega, 2020 - Ethiopia ³⁵	2014-2017	Retrospective cohort - 42 mo	179 (87)	ZDV	ART exp for at least 6 mo	Mean (SD) in years: 6.53 (2.83)	45%
Mega, 2020 - Ethiopia ³⁶	2015-2017	Retrospective cohort - 42 mo	179 (87)	ZDV	ART exp for at least 6 mo	Mean (SD) in years: 6.53 (2.83)	45%
Oshikoya, 2012 - Nigeria ³⁷	2008-2010	Retrospective cohort - 42 mo	80 (31)	At enrolment: ZDV-3TC + either NVP (92.5%), EFV (6.3%) or ABC-LPV/r (1.3%). Change in HAART regimen: n=33, including 31 with ABC	ART naïve	Median (IQR) in years: 3.0 (1.1- 6.0)	43%
Natukunda, 2017 - South Africa ³⁸	2014-2015	Cross-sectional study	501 (231)	Several, ABC-3TC-EFV (33%), TDF-FTC-EFV (23%)	ART-exp, 5 (2 - 10) yrs	Median (IQR) in years: 14 (12-16)	46%
Ahimbisibwe, 2020 - Malawi ³⁹	2018-2019	Cross-sectional study	806 (32)	No information on regimen, NRTI other than ABC: ZDV (78%) or TDF (18%), combined with EFV, LPV/r or NVP	ART exp for at least 6 mo	Median (IQR) in years: 10 (7-13)	53%

Wks=weeks, mo=months, yrs=years, ART-exp=ART experienced, ABC=abacavir, d4T= Stavudine, 3TC= Lamivudine, EFV=Efavirenz, TDF=Tenofovir, LPV/r=Lopinavir boosted ritonavir, ZDV=Zidovudine.

Table 2: Safety outcomes in children and adolescents treated with ABC-containing drug regimen, systematic review 2009-2020:

First author, year publication, age groups	Control group	Hypersensitivity reaction		Grade 3/4 adverse events		Mortality		Treatment discontinuation		Other morbidities and adverse events	
		ABC	Control	ABC	Control	ABC	Control	ABC	Control	ABC	Control
Mulenga, 2016 Children	d4T, ZDV	n=2, 1%	d4T: n=5 (3%) ZDV: n=1 (0.6%)	n=51, 31%	d4T: n=46 (29%) ZDV: n=53 (34%)	n=9 (5%)	d4T: n=7 (4%) ZDV: n=3 (2%)	/	/	Primary endpoint AE (i.e grade 2 or greater clinical AE, confirmed grade 3 laboratory AE, or any grade 4 laboratory AE) =64% Lipodystrophy=0% Mitochondrial disease=0.6%	<u>d4T</u> : Primary endpoint AE=67% Lipodystrophy=1% Mitochondrial disease=0.6% <u>ZDV</u> : Primary endpoint AE=65% Lipodystrophy=0% Mitochondrial disease=0%
Dirajlal-Fargo, 2017 Children	d4T, ZDV	/	/	/	/	Not reported	Not reported	/	/	Median change in Homeostatic model assessment of insulin resistance (HOMA-IR) at 48 wks: 6% (-34% to 124%)	<u>d4T</u> : Median change in HOMA-IR at 48 wks: 14% (-29% to 97%) <u>ZDV</u> : Median change in HOMA-IR at 48 wks: -1% (-30% to 69%)
Strehlau, 2018 Children	d4T	/	/	/	/	0	0	/	/	Lipodystrophy: n=5 (4.7%) WAZ (Mean± SD)=-0.72 ± 1.0 HAZ (Mean± SD)=-1.21 ± 1.0	Lipodystrophy n=17 (16.0%) WAZ (Mean± SD)=-0.72 ± 1.0, p=0.962 HAZ (Mean± SD)=-1.18 ± 1.0, p=0.851
Fortuny, 2014	NA	n=9 (8%)	/	n=22 (32%)	/	Not reported	/	n=4/109 (4%)	/	At least 1 AE: 39%, 42/109	/
Fortuin-De Smidt, 2017 Children & Adolescents	Most common: 3TC-d4T + either EFV or LPV/r	n=2 (0.2%)	Not reported	/	/	/	/	n=58, 30 (95%CI 23.3 to 39.4) per 1000 pat- yrs	n=841, 87 (95%CI 81.1 to 92.8) per 1000 pat- yrs	Treatment-limiting toxicity: n=3, 1.6 (95% CI 0.5 to 4.8) per 1000 patient yrs	Treatment-limiting toxicity: n=46, 50.6 (95% CI 46.2 to 55.4) per 1000 patient yrs aHR (ref ABC) =30.8 (95% CI: 4.3 to 220.2)
De Waal, CROI 2020 Infants	ZDV	n=1 (0.1%)	/	/	/	Not reported	Not reported	Over 12 mo: n=61/789 (8%)	Over 12 mo: HR=0.16 (95%CI 0.10-0.23)	/	/
Patel, 2012 Children	ABC use Yes vs No	/	/	/	/	/	/	/	/	Incident cardiomyopathy: 8 (8%)	Incident cardiomyopathy: 91 (92%), aOR (ABC use Yes vs No) =0.7 (0.3, 1.5)
Patel, 2014 Adolescents	ABC use Yes vs No	/	/	/	/	Not reported	/	/	/	Current use: Abdominal Aorta PDAY Score 0: n=29 (23%), ≥1: 17 (44%), aOR=1.77 (0.60-5.27)	/
Nahiry-Ntege, 2011 Infants, Children & Adolescents	NA	n=4 (0.3%)	/	/	/	n=46 (4%)	/	n=7/52 (13%)	/	Serious AEs: n=52 (4.5%), 40 within the first 4 wks of ART	/
Crichton, CROI 2020 Infants	NA	n=1 (0.7%)	/	n=8 (6%), all within the first 7	/	Not reported	/	By 12 mo: Due to ART safety: 4/139, cum	/	/	/

		days of ART						inc=3.6% (95%CI 1.4-7.8%) For any reason: 15/139, cum inc =11.8% (95%CI 7.3-18.9%)				
Pareek, 2019 Children & Adolescents	NA	0%	/	/	/	n=1 (2%) (not related to ABC HSR)	/	/	/	/	Side effects observed included fever (8, 16%), skin rash (7, 14%), respiratory symptoms (6, 12%), gastrointestinal symptoms (2, 4%), and constitutional symptoms (1, 2%)	
Manglani, 2018 Children & Adolescents	NA	n=2 (2%) Both HLA-B*5701 positive.	/	/	/	Not reported	/	/	/	/	/	
Chakravarty, 2016 Children	NA	n=8 (7.9%) 2 HLAB*5701 positive	/	/	/	/	/	/	/	/	Case 1 had a febrile illness, Case 2 & 3 had skin infections and Case 3 & 5 had concomitant pulmonary tuberculosis. All symptoms resolved after stopping ABC.	
Cassim, 2017 Infants	d4T	/	/	/	/	n=2 (3.5%)	n=9 (7.9%)	/	/	/	<u>At 6 months, median (IQR):</u> WAZ= -0.93 (-1.42,0.03) HAZ=-1.65 (-2.41,-0.67) <u>At 12 months, median (IQR):</u> WAZ= -0.70 (-1.25,0.17) HAZ=-1.91 (-2.64,-1.23)	<u>At 6 months, median (IQR):</u> WAZ= -1.18 (-1.95,0.03), p=0.18 HAZ=-1.58 (-2.65,-0.74), p=0.67 <u>At 12 months, median (IQR):</u> WAZ= -0.64 (-1.44,0.22), p=0.93 HAZ=-1.72 (-2.41,-0.73), p=0.25
Technau, 2013 Infants & Children	d4T, with either EFV or LPV/r	/	/	/	/	LPV/r: n=6 (3%), EFV: n=3 (1%)	LPV/r: n=24 (4%), EFV: n=25 (3%)	/	/	/	/	
Langs-Barlow, 2013 Children	Most common ZDV-3TC, + either EFV or NVP	/	/	/	/	Not reported	Not reported	/	/	/	Increased risk of positive EPF score for mitochondrial toxicity: ABC exposure: (OR = 4.76, 95% CI = 2.39-9.43)	
Mega, 2020 Children	ZDV	/	/	/	/	n=1 (1.1%), Median survival time =273	n=3 (3.3%), Median survival time =366 (86-676) days	/	/	/	Opportunistic infections: ABC +3TC + EFV (23/68) ABC + 3TC +LPV/r (5/15) ABC + 3TC + NVP (1/5) Pneumonia: 16/87 Incidence of OI: 8.8/100,000py	Opportunistic infections: ZDV +3TC + EFV (24/71) ZDV +3TC + LPV/r (5/15) ZDV + 3TC + NVP regimen (0) Pneumonia: 15/92 Incidence of OI: 6.9/100,000py

						(123-569) days	Not reported	Not reported		Incidence rate ratio=0.87, 95%CI 0.49-1.53, p=0.304
Oshikoya, 2012	ZDV-3TC + either NVP, EFV or ABC-LPV/r	/	/	/	/	Not reported	Not reported		Skin rash events: ABC-3TC-NVP, n=2/93 Gastrointestinal (vomiting, nausea, diarrhea, abdominal pains): ABC-3TC-LPV/r, n=7/31 ZDV-3TC-ABC-ddl-LPV/r, n=3/31 ABC-3TC-ZDVLPV/r, n=6/31 Pallor: ZDV-3TC-ABC-ddl-LPV/r, n=1/12 Headache: ABC-3TC-NVP, n=1/6 ABC-3TC-LPV/r, n=3/6 ABC-3TC-ZDVLPV/r, n=2/6	Skin rash events: ZDV-3TC-NVP, n=91/93 Gastrointestinal (vomiting, nausea, diarrhea, abdominal pains): ZDV-3TC-NVP, n=11/31 ZDV-3TC-EFV, n=2/31 Pallor: ZDV-3TC-NVP, n=9/12 ZDV-3TC-EFV, n=1/12 ZDV-3TC-LPV/r, n=1/12
Natukunda, 2017	several, ABC-3TC-EFV (33%), TDF-FTC-EFV (23%)	/	/	/	/	Not reported	Not reported		aOR >=3 self-reported symptoms: ABC-containing regimens (Y/N): 0.94 (0.53 - 1.67) <u>Association ABC with:</u> Skin rash: 0.65 (0.40 - 1.05) Diarrhoea: 0.62 (0.38 - 1.01) Nausea/vomiting: 0.99 (0.61 - 1.61) Stomach problems: 0.98 (0.60 - 1.60)	aOR >=3 self-reported symptoms: ZDV: 0.73 (0.35 - 1.52), TDF: 1.50 (0.71 - 3.21), D4T: 3.38 (1.19 - 9.60) <u>Association ZDV with:</u> Skin rash:1.38 (0.70 -2.72) Diarrhoea:1.01 (0.51 -2.00) Nausea/vomiting:0.58 (0.28 - 1.18) Stomach problems:0.97 (0.48 - 1.97) <u>Association D4T with:</u> Skin rash:0.58 (0.25 -1.35) Diarrhoea:1.57 (0.71 -3.48) Nausea/vomiting:2.47 (1.09 - 5.62) Stomach problems:1.41 (0.63 - 3.16) <u>Association TDF with:</u> Skin rash:1.17 (0.63 -2.17) Diarrhoea:1.07 (0.58 -1.99) Nausea/vomiting:1.14 (0.61 - 2.13) Stomach problems:1.04 (0.55 - 1.94)

Wks=weeks, mo=months, yrs=years, AE=Adverse Event, ART-exp=ART experienced, cum inc= cumulative incidence, OR= Odds Ratio, RCT=Randomised Clinical Trial, VL=VL, WAZ=Weight-for-age Z-score, HAZ=Height-for-age Z-score..
 ABC=abacavir, d4T= Stavudine, 3TC= Lamivudine, EFV=Efavirenz, TDF=Tenofovir, LPV/r=Lopinavir boosted ritonavir, ZDV=Zidovudine. "/" = outcomes not reported or no comparative group
Age groups: Infants = 0-12 months, Children = 1-10 years, Adolescents = 10-19 years

Figure

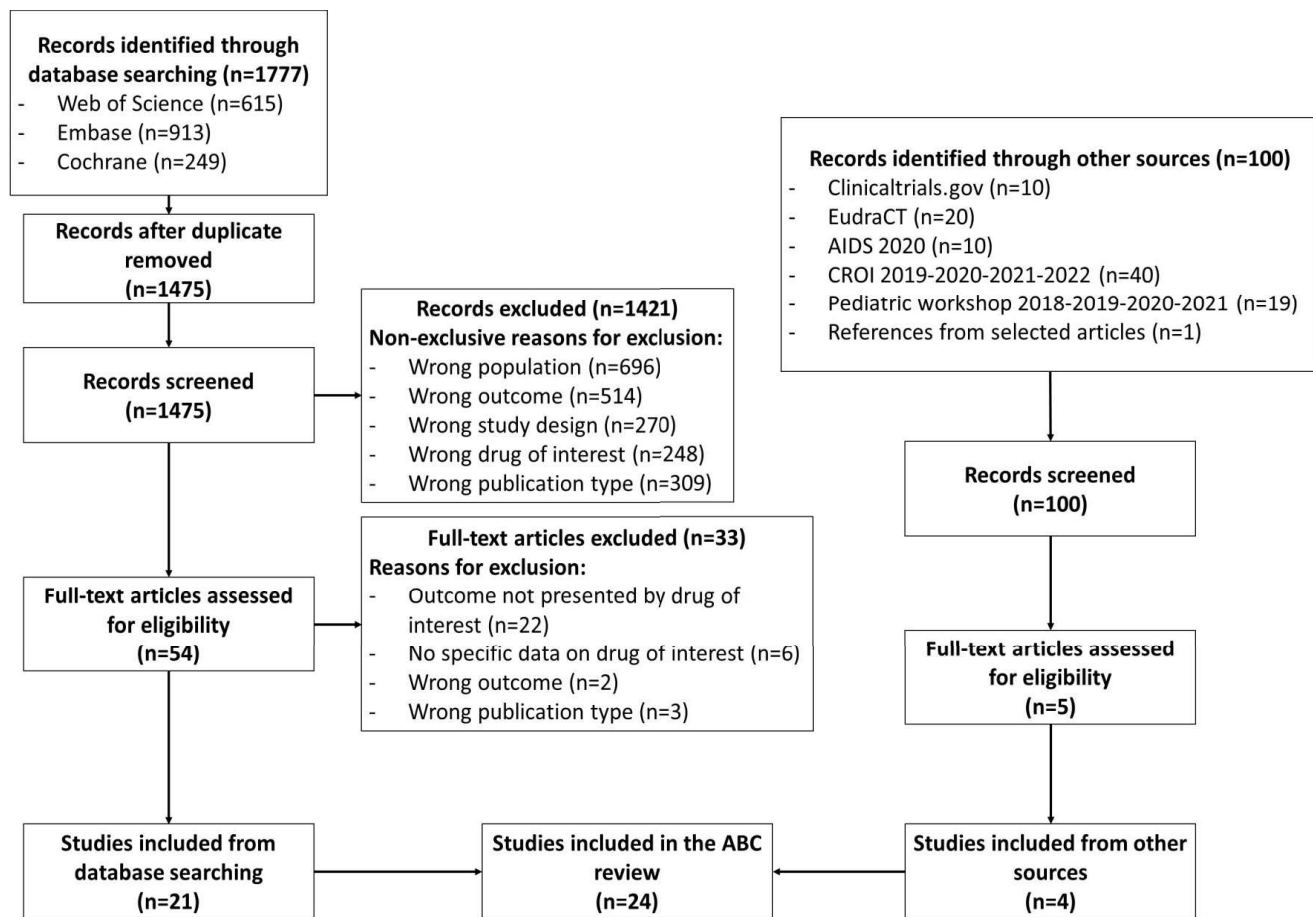


Figure 1: Study selection on ABC-containing regimen safety and effectiveness in children and adolescents living with HIV (2009-2022). One article was identified through database searching and other sources (AIDS 2020 published abstract)

Figure

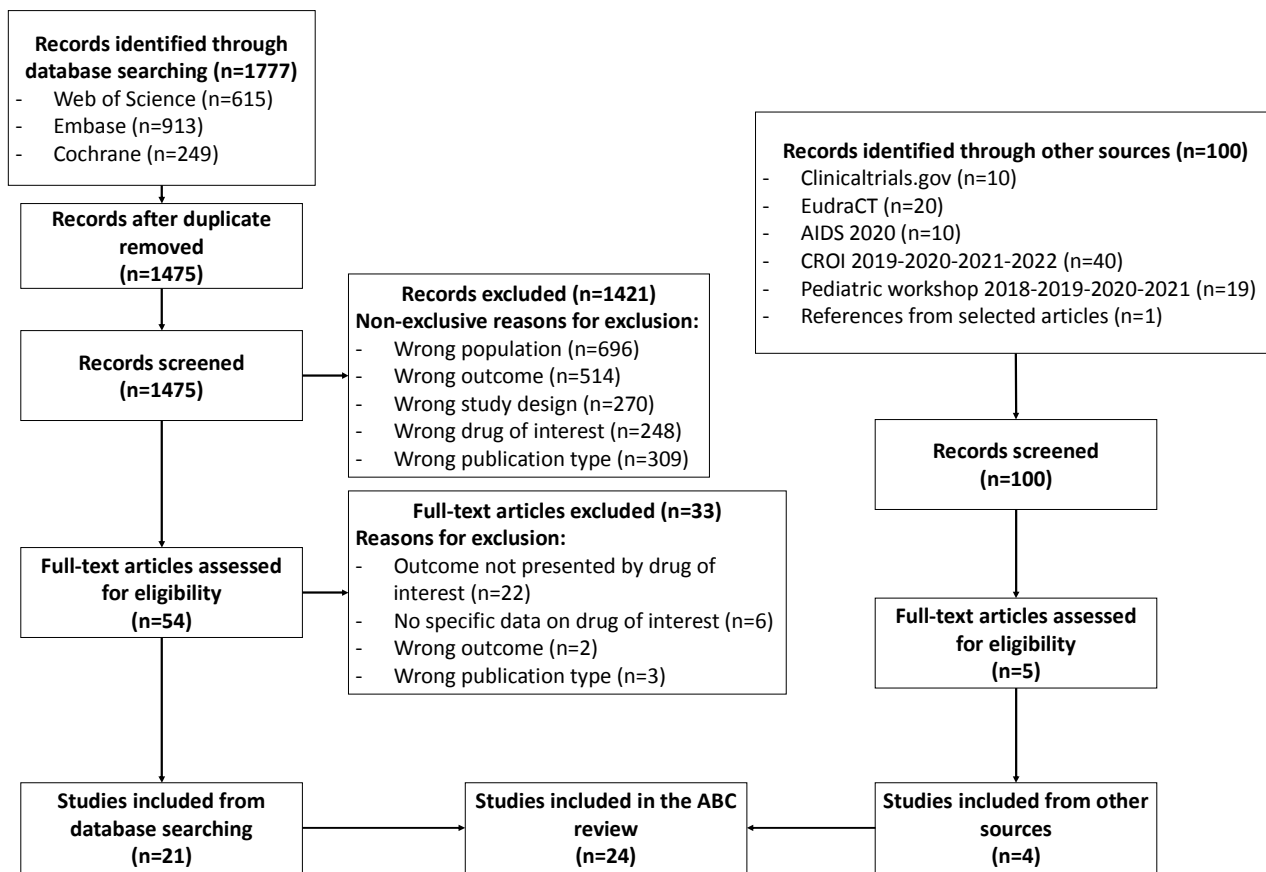
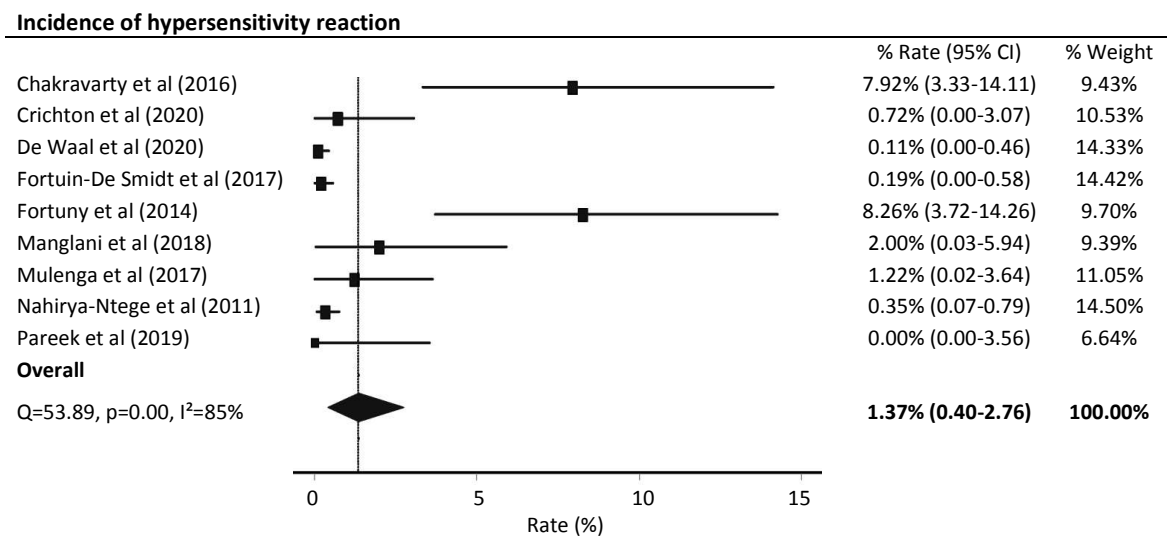
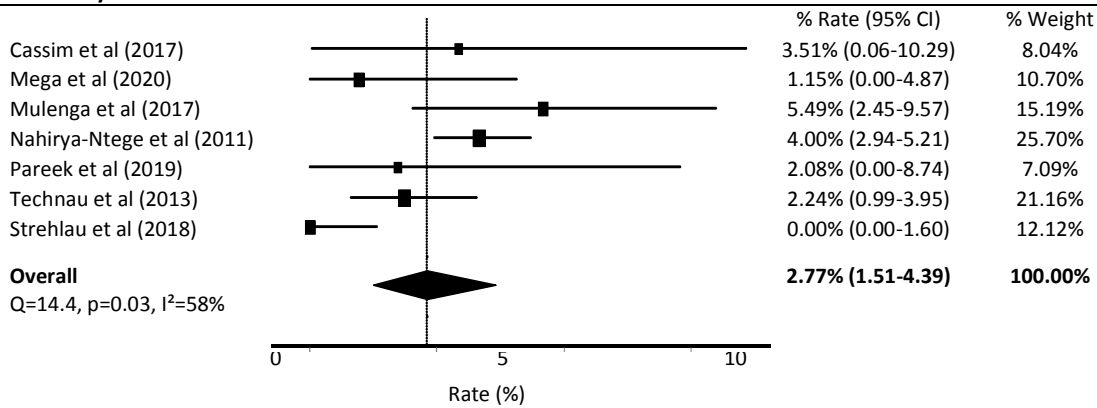


Figure 2: Cumulative incidences and pooled estimations for safety outcomes (hypersensitivity reaction and death) and effectiveness outcomes (viral load <400 copies/mL at 12 months) in children and adolescents treated with ABC-containing drug regimen



Mortality rate



Viral load suppression (<400 copies/ml) 12 months after ART initiation

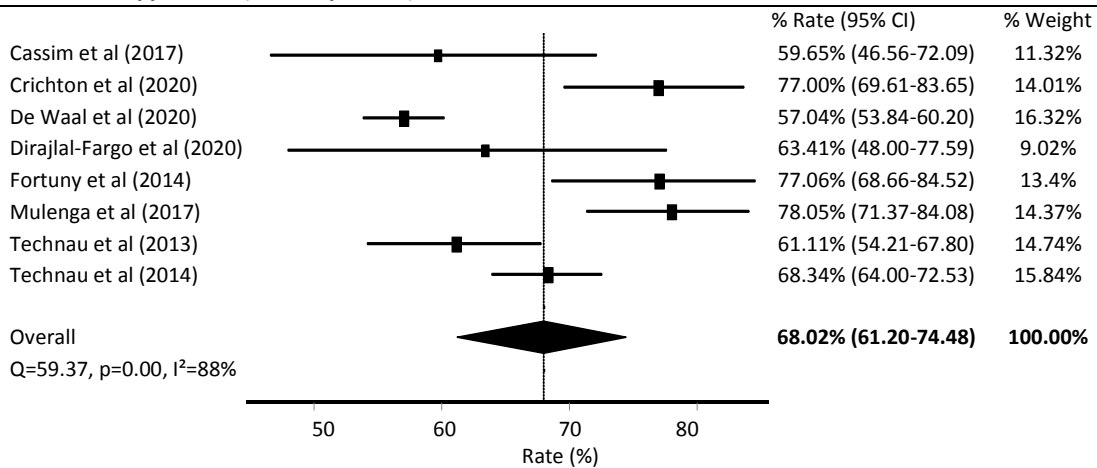
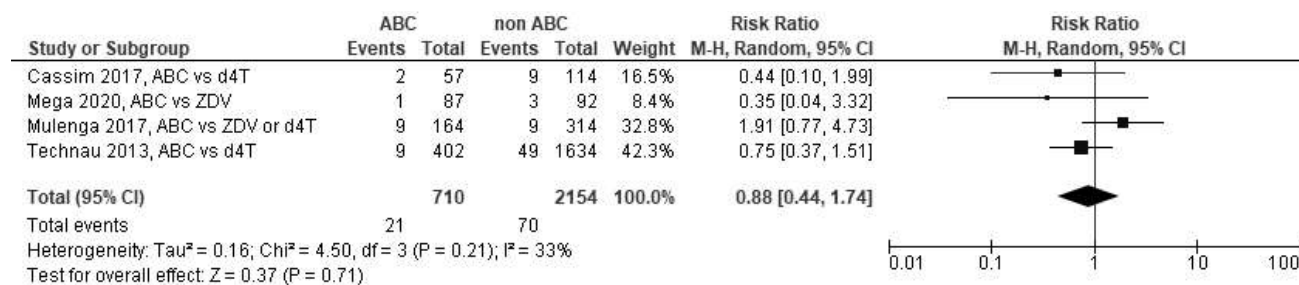
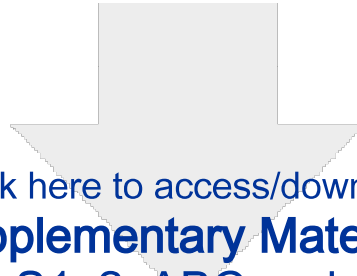


Figure 3: Relative risk ratio of mortality rate of children and adolescents treated with ABC-based drug regimen compared to non-ABC-based drug regimen



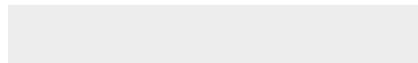
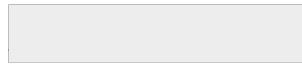
ABC=abacavir, d4T= Stavudine, ZDV=Zidovudine. M-H= Mantel-Haenszel



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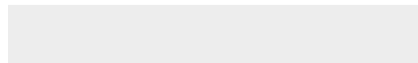




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