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The Use of Tenofovir Alafenamide Contained Regimens in Adolescents: Systematic Review

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ABSTRACT

Background: Adolescents living with HIV tend to experience worse immunological and viral suppression outcomes compared to adults, which in turn contributes to their higher mortality. In fact, adherence to antiretroviral therapy (ART) can be challenging for adolescents and then, poor adherence can increase their risk of drug resistance and virological failure. This is why single-tablet, once-daily HIV-treatment regimens with proven efficacy and effectiveness might address some of their adherence challenges in adolescents. Tenofovir alafenamide has favorable pharmacokinetic characteristics that offer the potential for a better safety profile, efficacy and it may be used in adolescents.

Objective: To investigate the effectiveness and efficacy of tenofovir alafenamide based regimens in adolescents. To determine the safety of tenofovir alafenamide contained regimens in adolescents. To verify short term adherence of tenofovir alafenamide based regimens in adolescents.

Methods: We conducted an electronic search on CENTRAL (Cochrane Central Register of Controlled Trials), Scopus, Web of science, EMBASE, PubMed, CINAHL and MEDLINE. We conducted a meta-analysis for outcomes with baseline data and we reported narratively other outcomes.

Selection criteria: Average age 6 to 18:

- HIV positive,
- On or initiating ART,
- ART safety and pharmacokinetics
- Reported adherence, viral load and/or CD4 count and eGFR creatinine outcomes,
- Randomized controlled trial (RCT) or trials.

Main results: Of 248 articles, 5 met inclusion criteria. The results have demonstrated both HIV-1 RNA and CD4 cells count were statistically enhanced in initiation stage. However eGFR improved in both adolescents who were switched to tenofovir alafemide contained regimens and those on initiation stage. Besides tenofovir alafemide based regimens have shown good pharmacokinetics, it has improved BMD and the sides effects were minimized in adolescents.

Conclusion: Based on the results, tenofovir alafemide based regimens could be efficient in ART initiation in adolescents. Therefore, this review should be taken in a context of limitations because of low sample sizes studies.

Keywords: Tenofovir alafenamide, Adolescents, HIV

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INTRODUCTION

Adolescents and young people represent a growing share of people living with HIV worldwide [1]. In 2017, 590,000 young people between the ages of 15 to 24 were diagnosed infected with HIV, of whom 250,000 of them were adolescents between the ages of 15 and 19 [1]. To compound this, most recent data indicate that only 23% of adolescent girls and 17% of adolescent boys aged 15-19 in Eastern and Southern Africa which are the region most affected by HIV [1]. Despite the increasing access to ART, numerous studies have demonstrated suboptimal levels of viral suppression in different populations in many low-resource settings [2,3]. In particular, adolescents living with HIV tend to experience worse immunological and viral suppression outcomes compared to adults [3-5], which in turn contributes to their higher mortality [3,6,7]. The current low rates of HIV diagnosis and treatment initiation among adolescents and young people ages 15-24 continues to present a significant challenge to the epidemic control of HIV [8]. With a 'business as usual' approach to HIV testing and linkage to treatment, new infections among adolescents and youth will likely increase, with the burden compounded by the increasing number of youth in Africa, expected to reach 293 million by 2025 [8]. In fact, adherence to antiretroviral therapy (ART) can be challenging for adolescents [9-11] and then, poor adherence may increase their risk of drug resistance and virological failure [11]. Maintaining medication adherence is vital to ensuring that adolescents living with HIV/AIDS receive the benefits of antiretroviral therapy (ART), although this group faces unique challenges to adherence [12]. Relevant studies revealed few consistent relationships between measured factors and adherence while highlighting potentially important themes for ART adherence including the impact of:

1. Adolescent factors such as gender and knowledge of sero-status,
2. Family structure,
3. The burdensome ART regimens, route of administration, and attitudes about medication, and
4. Health care and environmental factors, such as rural versus urban location and missed clinic appointments [12]. This is why single-tablet, once-daily HIV-treatment regimens with proven efficacy, effectiveness, safety and good pharmacokinetics might address some issue of the adherence challenges in adolescents.

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir that is converted intracellularly to the active form; the resulting concentrations of tenofovir diphosphate in circulating lymphocytes are higher than those achieved with tenofovir disoproxil fumarate (TDF). TAF has a similar antiviral efficacy to TDF at a lower dose, resulting in 91% lower plasma tenofovir exposures [13]. Additionally, TAF results in roughly four times higher intracellular concentrations of the active metabolite tenofovir-diphosphate compared with TDF, allowing for much lower doses of TAF versus TDF.11 Because of TAF's reduced dose and the improved stability, plasma exposure of tenofovir is 90% lower with TAF than with TDF, which is believed to reduce the risk of renal and bone toxicity [14]. TAF has favorable pharmacokinetic characteristics that offer the potential for a better safety profile than TDF and then it may be used in children and adolescents. Studies have shown that more than 90% of patients receiving TAF had virological suppression at week 48, but renal and bone abnormalities were significantly reduced in patients allocated to TAF compared with those allocated to TDF [14,15]. A recent review demonstrated that Evidence for the benefit of TAF over TDF in reducing HIV-RNA and HBV DNA, increasing CD4 cells, preventing CKDs and loss of bone mineral density should be recommended in HIV or/and Hepatitis B therapy and preventing TDF related toxicity [16].

The switch to TAF also resulted in improvements in renal function, including decreases in serum creatinine (those switching from a boosted regimen), decreases in dipstick proteinuria, decreases in quantitative tests of total urine protein, and total urine albumin, decreases in specific proximal renal tubular proteins, and improvements in tests of proximal renal tubular function (fractional excretion of uric acid, fractional excretion of phosphate, and renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate). Proteinuria, albuminuria, and specific proximal tubular proteinuria have been shown to increase risk of mortality or cardiovascular events in both the general population and in HIV-1 infected individuals [15,17,18]. Several studies on TAF based regimens have been conducted in adults, however data are scared in adolescents and this is the first review in this field that has conducted in this adolescents HIV infected.

METHODS

The review protocol was registered with international prospective register of systematic reviews (PROSPERO) (identification number: CRD42017070486). This protocol could be found online at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017070486

Electronic search

We conducted an electronic search on CENTRAL (Cochrane Central Register of Controlled Trials), Scopus, Web of science, EMBASE, PubMed, CINAHL and MEDLINE. Additionally, HIV conferences web sites such as the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS) The following search strategy was used: HIV explode all trees

AND (HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV infect* OR human immunodeficiency virus OR human immune-deficiency virus OR human immuno-deficiency virus OR human immun* deficiency virus OR acquired immunodeficiency syndrome) AND (Adolescents OR young adults OR teenages) AND (Tenofovir alafenamide OR tenofovir prodrug OR TAF OR GENVOYA OR DESCOVY®) AND (Randomized controlled trial) OR (controlled clinical trial) OR (randomized controlled trials) OR (random allocation) OR (double-blind method) OR (single-blind method) OR (clinical trial) OR (trial) OR (clinical trials) OR (clinical trial) OR (singl* OR doubl*) OR (trebl* OR tripl*) AND (mask* OR blind*) OR (placebos) OR (placebo*) OR (random*). We identified works published through October 11, 2018. Inclusion criteria were focus on the following:

1. Average age 6 to 18,
2. HIV positive,
3. On or initiating ART,
4. ART safety
5. Reported adherence, viral load and/or CD4 count and eGFR creatinine outcomes,
6. Randomized controlled trial (RCT) or trials.

Selection of articles for review

As presented in **Figure 1**, 248 articles were identified by the applied the above search strategy. Title and abstract review excluded 202 articles; complete text review eliminated another 174. In full, only 5 articles met all criteria. Among them, one article was an ongoing trial and then 4 articles were used in data synthesis **(Figure 1)**.

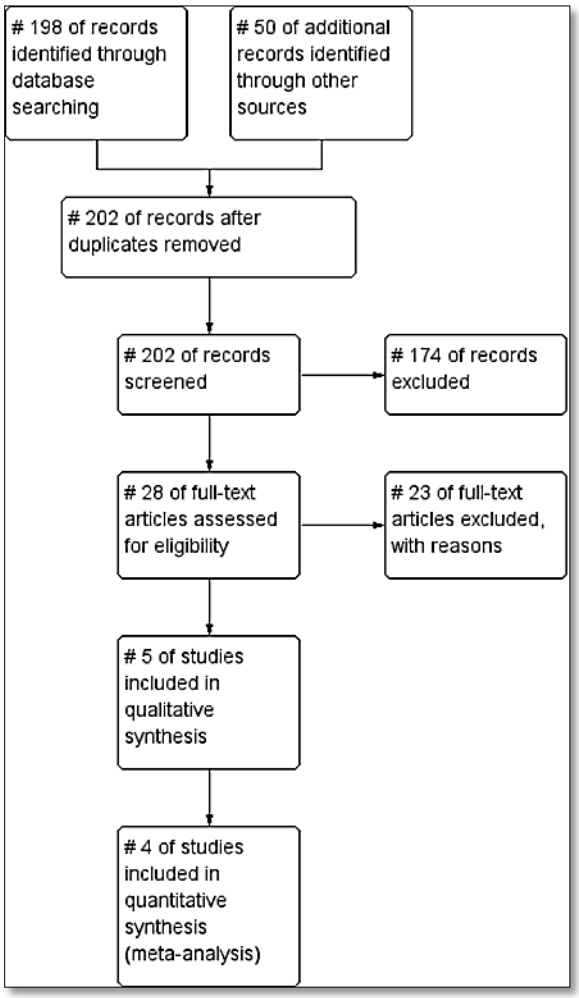

Figure 1. Study flow diagram.

Data extraction

Each article that met selection criteria was critically appraised for baseline characteristics of the population included in the research (e.g. age, sample size, viral load, CD4 count, eGFR, weight and ART regimens), study design (e.g. Phase 2/3, open-label, multicenter, multi-cohort, single-

arm study), intervention characteristics/adherence strategies in treatment condition (e.g. TAF contained regimen, duration, dosage and targets), outcomes measured (HIV-1 RNA, CD4, eGFR, changes in bone mineral density, pharmacokinetics, adverse events and adherence), methodology for and frequency of outcomes measurement, overall outcome of evaluation as reported in article. Those information were extracted by two authors (JT and VK) and recorded in an excel worksheet database. Additionally, the risk of bias was assessed in each study and reported in the excel worksheet.

Data synthesis

In on hand, meta-analysis was undertaken for studies with less diversity. The baseline characteristics were roughly considered when we conducted data synthesis. We reported binary outcome (HIV-1 RNA) by using the odds ratio and its 95% CI. And, continuous outcomes (CD4 count and eGFR) were reported with the mean difference and the 95% CI. We used the Cochrane's Review Manager Software (RevMan 2014) to conduct meta-analysis. When interventions and study populations were sufficiently similar across the different studies, we pooled the data across studies and estimate summary effect sizes using both fixed- and random effects models.

GRADE evidence profiles and summary of findings tables was generated with GRADEpro software. Diversity between included studies was assessed with the I2 test. The results were considered as statistically significant when P-value <0.05. In the other hand, we reported narratively four outcomes (any AE, serious AE, ART adherence, Changes in Bone Mineral Density (BMD) and pharmacokinetics (PK) parameter. Data extracted from each trial were summarized and iteratively reviewed by both authors (JT and VT) to identify common themes and limitations in the current evidence base.

RESULTS

Populations

5 articles met inclusion **(Table 1)** and represented a total of 176 adolescents. The average enrolled sample size was about 44 participants per study. The minimum and maximum sample sizes were 37 and 50, respectively. These sample sizes were small and then the studies powers were low. Two studies reported HIV infected, virologically suppressed adolescents and two others included HIV infected adolescents with high viral load. The baseline CD4 count cells varied between 100 to 200 cells/µl, eGRF (Schwartz formula) was ≥ 90 mL/min/1.73 m^2 and the weights were above 25 and 35 kg.

Table 1. Included studies: The use of Tenofovir alafenamide contained regimens in adolescents: Systematic review.

Study ID	Title	Sample	Design	Intervention description	Baseline Characteristics	Outcomes
Chen [19]	Safety, Pharmacokinetics, and Efficacy of FTC/TAF in HIV-Infected Adolescents (12-18 Years)	Screened: N=37; enrolled: N=28 Cohort 1: HIV-1 infected, virologically suppressed adolescents; aged 12-18 years; weight ≥ 35 kg–HIV-1 RNA<50 copies/mL for ≥ 6 mo on a stable regimen of 2 NRTIs with various 3rd	Phase 2/3, open-label, multicenter, multicohort, single-arm study	FTC/TAF 200/10 mg qd with boosted or 200/25 mg qd with unboosted 3rd ARVs for 24 weeks	HIV-1 RNA <50 copies/mL:27/28 Mean(SD) CD4 cell count/µL: 909 (242.7) Mean CD4 % (SD): 36.1 (6.40) Mean(SD)eGFR, mL/min/1.73 m^2: 160.25 (12.55)	HIV-1 RNA <50 copies/mL: 26/28 Mean (SD) CD4 count/µL: 779 (255.1) Any AE: 24 (86) Serious AE n (%): 2 (7) Mean 93% (SD 10%) adherence Adherence: 20/28

		antiretroviral (ARV) agents - CD4 count ≥ 200 cells/µL eGFR; Schwartz formula) ≥ 90 mL/min/1.73 m^2				Median % change in BMD: +3.56
Gaur [11]	Safety, efficacy and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial	50 adolescents HIV+ from ten hospital clinics in South Africa, Thailand, Uganda and the USA. Aged 12-18 years, with HIV-1 RNA=<1000, CD4 count=<100 cells/µL and eGFR=<90 mL/min per 1·73 m² Schwartz formula, BW=<35 kg	An open-label, single-arm, two-part trial	A single-tablet regimen once per day, containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide. Study visits to the clinic occurred at weeks 1, 2, 4, 8, 12, 16, 24, 32, 40 and 48.	HIV-1 RNA>100 000 copies/mL: 11/50 Mean (SD) CD4 count: 471 (212·2) cells per µL Mean (SD) eGFR (Schwartz; mL/min per 1·73 m²): 174.25 (45.75)	HIV-1 RNA<50 copies per mL: 46/50 CD4 Mean (SD): 685 cells per µL (245·4) Mean (SD)eGFR mL/min per 1·73 m²: 160.525 (38.125) Median % change in BMD: +3·3% (IQR 0·8 to 7·1 Any AE: 42/50 Any serious AE: 4/50
Kizito [20]	Week 24 data from a Phase 3 clinical trial of E/c/f/taf in HIV-infected	48 HIV-infected treatment-naïve adolescents (12-18 years); with HIV-1 RNA ≥	Phase 2/3, single-arm, open-label, two-part study	E/C/F/TAF for 24 weeks	HIV-1 RNA: ≤ 100,000 copies/mL: 38/48 > 100,000	HIV-1 RNA<50 copies/mL: 21/23 Mean

	adolescents	1000 copies/mL; genotypic sensitivity to EVG, FTC and TFV; CD4 count >100 cells/uL, HBV and HCV negative; eGFR (Schwartz formula) ≥ 90 mL/min/1.73m^2; Weight ≥ 35 kg			copies/mL: 10/48 Mean (SD) CD4 Count cells/µL: 527.25 (253.75)	(SD)CD4 cells counts/µL: 620 (254.6) Mean (SD) eGFR (Schwartz), ml/min/1.73 m^2: 148.0 (21.2) AE:81.3% (39) Serious AE: 8.3% (4)
Natukunda [21]	Safety, efficacy and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial	Population aged from 6 to <12 Years; Weight>=25 kg, HIV-1 RNA<50 copies/ml for 6 months; CD4 counts>=200 cells/µl; eGFR: >=90 ml/min/1.73 m^2 (Schwartz)	phase 2/3 open-label, multicentrer, multicohort, single arm study	ABC/3TC; ZDV/3TC with PI and NNRTI switching to Bictegravir/F/TAF	HIV-1 RNA < 50 Copies/ml: 50/50 Mean CD4 cell count/µl (SD): 930 (309.9) Mean (SD) eGFR ml/min/1.73 m^2: 156 (7.25)	HIV-1 RNA<50 copies/ml: 25/26 Mean (SD) CD4 cell count/µl: 830 (SD=257.4 Mean (SD) eGFR ml/min/1.73 m^2: 137 (5.9) Any grade AE (n%): 33 (66%) Adherence: Median (Q1, Q3): 98.8% (97.4%, 100%)

All studies were conducted in United State of America. Samples were small, resulting to low power studies. The average age of intervention participants ranged from 6 to 18 years of age.

Study designs

This review included 2 trials with phase 2/3, open-label, multicenter, multi-cohort, single-arm study, an open-label, single-arm, two-part trial, Phase 2/3, single-arm, open-label and a two-part study. Most of the interventions conducted repeated measures from baseline, generally including 2, 4, 8, 16 and 24 weeks assessments of outcomes. Only one trial measured the outcomes until 48 weeks.

Interventions

Interventions and the length of interventions incorporated in different studies varied, even though all trials encompassed TAF. FTC/TAF 200/10 mg qd with boosted or 200/25 mg qd with unboosted 3rd ARVs for 24 weeks[19], 150 mg elvitegravir, 150 mg cobicistat, 200 mgemtricitabine, and 10 mg tenofovir alafenamide for 48 weeks [11]. E/C/F/TAF for 24 weeks [20] and Bictegravir/F/TAF for 24 weeks [21] were different TAF contained regimens included in this study.

Outcomes

Meta-analysis was undertaken for the outcomes HIV1-RNA<50 copies/ml, CD4 cells and eGFR **(Figures 2-6)**. BMD, AE, serious AE and pharmacokinetics parameters were reported narratively. Chen [19] reported 86% of any AE and 7% of serious AE. ART adherence over 24 weeks was estimated to 74.4% and the median % change in BMD increase to +3.56% compared to the baseline. Gaur [11] found that any AE and serious AE were respectively 84% and 8%. Additionally, this study reported an increased median % change in BMD of +3.3%. Kizito [20] has shown any AE percent of 81.3 and Serious AE percent of 8.3%. Lastly, Natukunda [21] trial reported 66% of any AE and the median adherence of 98.8% in adolescents. Two studies reported clearly the area under the plasma drug concentration curve (AUC) comparing adolescents to adults. Chen [19] reported the mean (% CV) FTC AUCtau values were 14,300 (42.5) h·ng/mL in FTC/TAF 200/25 mg group and 14,800 (30.3) h·ng/mL in FTC/TAF 200/10-mg group. Kizito [20] reported the mean (% CV) AUC tau, ng*h/mL in E/C/F/TAF of 23840 (25.5). Reviewing all those parameters, the report has demonstrated that the results within the range were quite similar with safety, efficacy and pharmacokinetics in adolescents and adults.

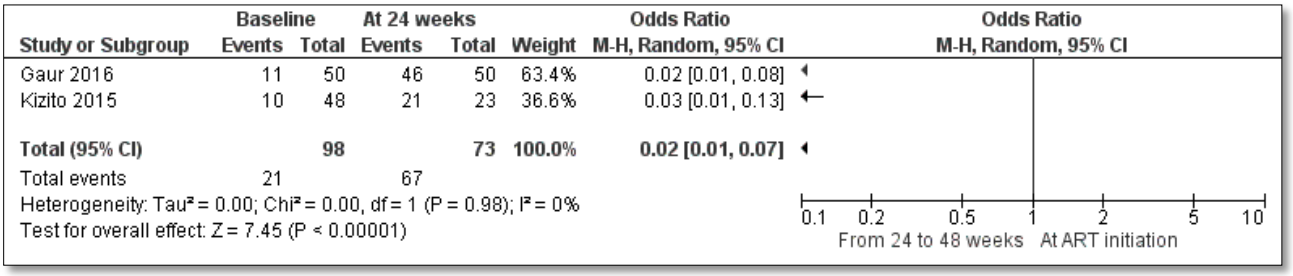

Figure 2. Meta-analysis of TAF based regimens in initiation stage.

Outcome: HIV1-RNA

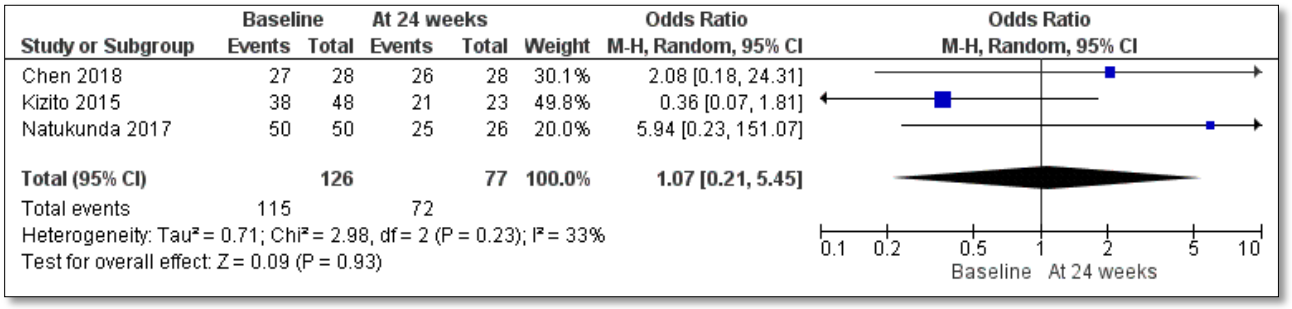

Figure 3. Meta-analysis of TAF based regimens when switching ART regimens.

Outcome: HIV1-RNA

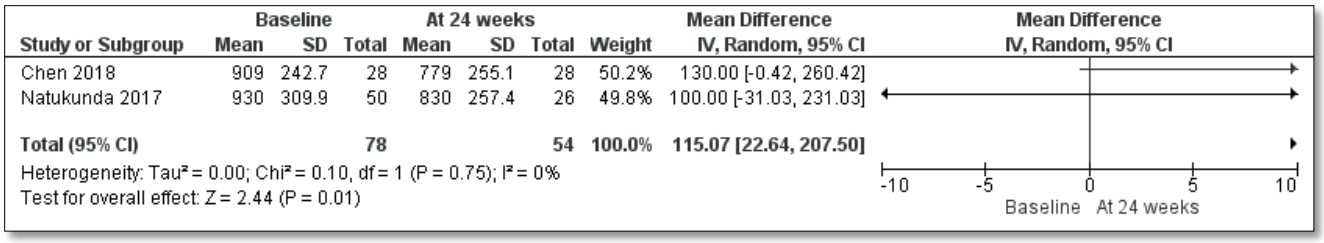

Figure 4. Meta-analysis of TAF based regimens in initiation stage.

Outcome: CD4 cells count

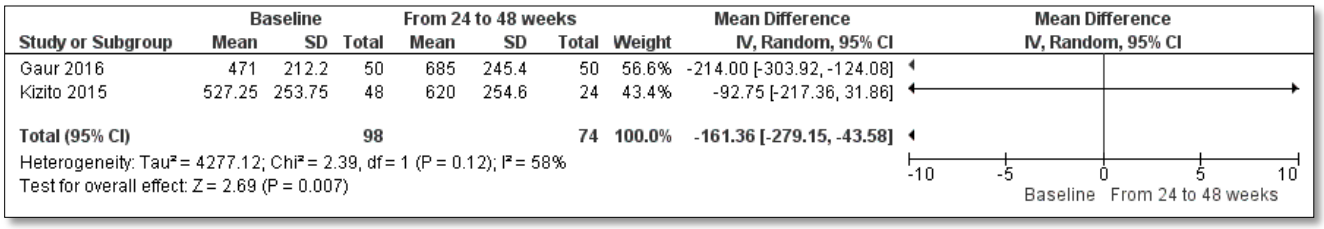

Figure 5. Meta-analysis of TAF based regimens when switching ART regimens.

Outcome: CD4 cells count

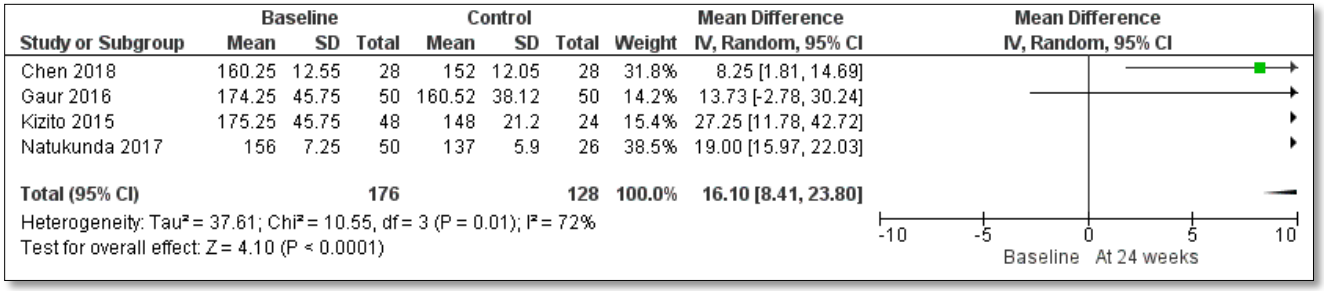

Figure 6. Meta-analysis of TAF based regimens.

Outcome: eGFR

Meta-analysis

HIV1-RNA<50 copies/ml: 2 trials with HIV1-RNA>10000 copies/ml in the baseline were included. From 24 to 48 weeks, the random effects meta-analysis of HIV-infected adolescents from the baseline to 24 to 48 weeks on TAF contained regimens reduced the HIV1-RNA by 20% with 95% CI 10% to 70%. This result was statistically significant with p-value <0.00001 **(Figure 2)**.

HIV1-RNA<50 copies/ml: 3 trials included HIV1-RNA<50 copies/ml in the baseline. In fact, Kizito [20] included both adolescents with HIV1-RNA<50 and >10000 copies/ml. The effect of TAF contained regimens from the baseline to 24 weeks was not statistically significant with OR 1.07 (95% CI 0.21 to 5.45, 7 studies, P=0.93) **(Figure 3)**.

CD4 cells count/µL: 2 studies included CD4 count cells and HIV1-RNA baseline characteristics were quite similar [19,21]. At 24 weeks, TAF contained regimens improved the mean difference of CD4 count cells (MD 115.07 95% CI 22.64 to 207.50, P-value=0.01) **(Figure 4)**.

CD4 Cells count/µL: 2 studies included CD4 count cells and HIV1-RNA baseline characteristics were quite similar [11,20]. From 24 to 48 weeks, TAF contained regimens decreased the mean difference of CD4 count cells (MD -161.36 95% CI -279.15 to -43.58, P-value=0.007) **(Figure 5)**.

eGFR ml/min/1.73 m^2 Schwartz: For 4 trials included in estimated glomerular filtration rate from the baseline and 24 weeks post TAF contained regimens. The baseline characteristics were homogenous enough and then, we conducted meta-analysis. The inverse variance and the random-effects meta-analysis of glomerular filtration rate yielded a pooled MD estimate of 16.10 (95% CI 8.41to 23.80, P<0.01) with I^2=72% **(Figure 6)**.

DISCUSSION

This review was conducted in a population aged from 6 to 18 years. In fact, tenofovir alafenamide regimens in this range of age are a new approach of HIV-1 treatment. Until now, they are not many trials undertaken in this field. Nonetheless, our review provides further evidence that TAF based regimens could be a new perspective of HIV treatment from 6 to 18 years old. Improvements in HIV-1 RNA, CD4 count, eGFR and BMD have proven the efficacy of TAF

based regimens in adolescents after 24 to 48 weeks of treatment. Additionally, the AE and serious AE were minimized with low percent. Lastly, AUCtau was quite similar to adults in two studies. This suggests that TAF contained regimens have same pharmacokinetics both in adolescents and adults. The results were mostly superior when the baseline characteristics were adolescents in ART initiation stage. We did not find any statistical significant results in adolescents switched from other ARV regimens to TAF based regimens. This may induce immunological failure. This is why, in clinical practice, we suggest that TAF based regimens should be switched with precaution in adolescents. Comparatively to adults, switching to ART regimens to TAF based regimens has demonstrated many benefits in HIV outcomes [16].

This present review should be taken in a context of several limitations. As the fact, the study was graded from moderate to low evidence. In fact, the sample sizes were low in all trials, resulting to low powers. Furthermore, the variations between the baseline characteristics and different TAF contained regimens included in trials implied indirectness between studies. Besides, the applicability could face some challenges as all studies were conducted in US. Knowing Sub Saharan African has the highest HIV adolescents HIV prevalence, and this rate is expected to increase in the future even though, other HIV infected class group is decreasing. Thus, large trials in this field should be conducted in Sub Saharan African so that TAF based regimens may find its clear applicability in adolescents.

CONCLUSION

In summary, TAF based regimens could play an important role in ART initiation, as first line in adolescents. Those regimens have demonstrated their efficacy in improving HIV outcomes in adolescents. But, large trials should be done to prove long term clinical significance of TAF based regimens in adolescents and also, to increase the study powers.

ACKNOWLEDGMENT

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