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Tenofovir alafenamide versus Tenofovir disoproxil: systematic review and meta-analysis (protocol).

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Abstract

Highly active antiretroviral therapy (HAART) has greatly reduced morbidity and mortality, resulting in high survival rates among infected patients. Despite the impact of HAART, mortality in successfully treated HIV infected patients remains higher than in the general uninfected population. The effects of persistent inflammation and drug toxicity on comorbidities that are considered non-HIV related, including metabolic, cardiovascular and renal disease, contribute to these differences in the health of infected individuals New Reference. Among antiretroviral moleculars, tenofovir disoproxil is widely used.

Tenofovir alafenamide is a new oral prodrug of tenofovir, a nucleotide analogue that inhibits HIV-1 transcription. Tenofovir alafenamide has potential intracellular accumulation; lower extracellular exposures of tenofovir may be realized with the potential to reduce off-target toxicities. Specifically, lower drug exposures to kidney cells may provide for fewer renal complications as observed in a minority of patients treated with tenofovir disoproxil fumarate.

Objectives

- To investigate whether Tenofovir alafenamide based regimens are less nephrotoxic than Tenofovir disoproxil based regimens.
- To evaluate whether Tenofovir alafenamide contained regimens could decrease mineral bones loss.
- To investigate the efficacy of TAF in co-infection HIV/hepatitis.

Search methods: We will search the following electronic databases: CENTRAL (Cochrane Central Register of Controlled Trials), Scorpus, Web of science, LILACS, PubMed and CINAHL. We will also search conference abstract archives on the web sites of 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).

Analysis: If include studies are as similar as possible, we will undertake meta-analysis using Cochrane's Review Manager Software (RevMan 2014). If included studies are heterogeneous, the results will be summarized in a narrative manner. GRADE evidence profiles and summary of findings tables will be generated.

Conclusion: This study could influence HIV management. TDF is largely used as first line regimen in HIV management. Therefore toxicity is restricted its use. This systematic review will find out whether TDF could be swift by TAF when TDF is contraindicated.

Key words: tenofovir alafenamide, tenofovir diproxil, HIV

Background

Description of the condition

HIV epidemic still carries a huge burden of morbidity and mortality in a large part of the world, and according to the estimates of the Joint United Nations Programme on HIV/AIDS (UNAIDS), 36.7 million [34.0 million – 39.8 million] people worldwide were living with HIV (UNAIDS 2016). In the same year 2.1 million [1.8 million – 2.4 million] people were newly infected with HIV and 1.1 million [940 000 – 1.3 million] died from acquired immunodeficiency syndrome (AIDS)-related causes (UNAIDS

2016). Highly active antiretroviral therapy (HAART) has greatly reduced morbidity and mortality, resulting in high survival rates among infected patients (Mocroft 1998, Palella 1998, The Antiretroviral Therapy Cohort Collaboration 2008, Kitahata 2010). Despite the impact of HAART, mortality in successfully treated HIV infected patients remains higher than in the general uninfected population (Bhaskaran 2008). The effects of persistent inflammation and drug toxicity on comorbidities that are considered non-HIV related, including metabolic, cardiovascular and renal disease, contribute to these differences in the health of infected individuals. Among antiretroviral moleculars, tenofovir disoproxil is widely used. In fact, Tenofovir disoproxil fumarate (TDF) containing combination antiretroviral therapy (ART) is currently considered a first-line regimen for HIV treatment and prevention of mother-to-child transmission (PMTCT) Option B/B+ by the World Health Organization (WHO) (WHO 2013). In addition, TDF is the approved drug for pre-exposure prophylaxis (PrEP) (European AIDS Clinical Society 2014, Pinto 2016).

Therefore, a systematic review has identified 17 studies that TDF containing ART regimens were associated with a significantly greater loss of kidney function than were ART regimens not containing TDF. Furthermore, the review also found a significantly higher risk of acute renal injury associated with TDF use. Nonetheless, debate continues over whether more widespread use of TDF, particularly in "real world" clinical settings, might yet reveal a risk for nephrotoxicity significant enough to limit its use or to necessitate close clinical monitoring (Gupta 2005; Sax 2007; Cooper 2010). Furtheromre, previous studies have reported several risk factors for TDF-induced nephrotoxicity, including high basal serum creatinine (Cr) level, concomitant use of nephrotoxic drugs, low body weight, old age, and low CD4+ T cell count (Nelson 2009, Jin 2015). It is presumed that proximal tubule damage, diabetes insipidus, decreased bone density, and reduced glomerular filtration rate (GFR) could also occur in association with TDF use (Sax 2003, Wood 2009, Jin 2015). In addition, combinations of protease inhibitors (PI), such as atazanavir (ATV) or lopinavir (LPV), can an additional decrease in GFR,

compared to a combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI), such as efavirenz (EFV) (Goicoechea 2008, Young 2012, Jin 2015).

HIV-related renal diseases are one of the leading causes of chronic kidney diseases (CKDs) worldwide (Antonello 2015). In particular, the new era of highly active antiretroviral therapy (HAART) and early HIV diagnosis has improved survival and disease progression, leading to a higher proportion of patients with renal abnormalities over time(Szczech 2002, Banerjee 2014, Antonello 2015). CKD is defined by a sustained change in urinary sediment, such as the presence of proteinuria, or by a reduced glomerular filtration rate (GFR) (Antonello 2015). Nephrotoxicity can appear either during long or short-term use of TDF (Antonello 2015). TDF-induced nephrotoxicity is reported in about 15% of patients treated with TDF for 2–9 years (Quinn 2010, Jin 2015). Tenofovir is specifically a nucleoside reverse transcriptase inhibitor that can cause acute kidney injury (AKI), proximal tubular dysfunction, or both in combination (Antonello 2015). In addition, interstitial nephritis, renal tubular damage, and nephrolithiasis have been detected as renal complications of HIV infection (Roling 2006, Jin 2015). Proteinuria is often the earliest manifestation of CKD and is more common in HIV-infected individuals than in similarly aged HIV-negative controls (Antonello 2015).

Description of the intervention

Tenofovir alafenamide(TAF) is a new oral prodrug of tenofovir, a nucleotide analogue that inhibits HIV-1 transcription (Markowitz 2014). TDF, the first approved oral prodrug of tenofovir, has been used in combination antiretroviral therapy for the treatment of HIV-1 infection since 2001(American food 2001, Markowitz 2014).Hence, TAF is more stable in plasma than tenofovir disoproxil and then is specifically converted into tenofovir within cells by the cellular enzyme cathepsin A, which is highly expressed in lymphoid tissues (Satake 1997; Birkus 2007). Tenofovir is then further metabolized intracellularly to the active metabolite, tenofovir diphosphate, a competitive inhibitor of HIV-1 reverse transcriptase that terminates the elongation of the nascent viral cDNA chain (Markowitz 2014). Given the intracellular mechanism of activation of

TAF and potential for intracellular accumulation, lower extracellular exposures of tenofovir may be realized with the potential to reduce off-target toxicities (Markowitz 2014). Specifically, lower drug exposures to kidney cells may provide for fewer renal complications as observed in a minority of patients treated with TDF and the ability to dose TAF in patients with renal impairment without dose adjustment (Cooper 2010; Szczech 2002; Markowitz 2014).

How the intervention might work

TAF was identified as an alternate TFV prodrug to TDF that more efficiently loads HIV-target cells (Lee 2005). TAF is 1000- and 10-fold more active against HIV in vitro than TFV or TDF, respectively (Margot 2016). Reflecting the release of the same pharmacologically active metabolite, TAF has the same resistance profile as TFV and TDF in vitro but the higher PBMC levels achieved after TAF administration relative to TDF in patients (discussed further below) suggest better coverage of resistance mutations in the clinic (Margot 2016). Stability in biological matrices, including plasma, and selective intracellular cleavage of TAF allows for prolonged systemic exposure to intact prodrug and the accumulation of higher intracellular levels of the pharmacologically active metabolite TFV-DP relative to TDF(Margot 2016). In whole blood, TAF was found to preferentially load PBMC over red blood cells and formation of TFV and its phosphorylated metabolites was preceded by the intracellular formation of the key intermediate TFV alanine (Eisenberg 2001). Studies in isolated cells have shown efficient TAF activation and potent antiviral activity in the HIV-target cells CD4þ Tcells and monocyte derived macrophages (Bam 2014).

Following dosing with TAF, the resulting systemic exposure to TFV is 91% lower than is the case for an equipotent dose of TDF (Ruane 2013; Sax 2015). The majority of intact TAF transits directly into its lymphoid cell target, where it is then converted intracellularly to tenofovir diphosphate (Lee 2005,Babusis 2013; Birkus 2007). This in-target cell conversion of prodrug minimizes systemic exposure to TFV. Studies are ongoing to further explore intracellular drug levels in potential target tissues, which are important to the

understanding of the antiviral activity and safety of TAF and TAF containing regimens (Antela 2016). It is also possible to reduce the oral dose of TAF further through the use of boosted regimens containing (for example) cobicistat, an agent that inhibits the intestinal P-glycoprotein (P-gp) transporter, so allowing better absorption of TAF from the gastrointestinal tract (Babusis 2013, Antela 2016).

Why it is important to do this review

This systematic review is crucial in its genre. It will be a turnover in changing the use of TDF disopoxil to TAF, decreasing then nephrotoxicty due to tenofovir based regimens in both HIV-infected and not infected with HIV in the case post exposure prophylaxis. In addition, other fields will be investigated among which viremia, bone mineral density and serum cholesterol.

Lastly, the evidence to date suggests that this TAF-containing regimen offers high virological success rates that are similar to those of TDF-based regimens, with a more favorable safety and tolerability profile, characterized by less impact on multiple measures of renal function and less impact on BMD in both treatment-naive and treatment experienced patients (Antela 2016). Indeed, data from studies in virologically suppressed patients with either normal renal function or mild to moderate renal impairment (eGFR 30–69 mL/min), suggest that TAF may offer TFV-equivalent potency together with an improved renal and bone safety profile (Antela 2016).

Objectives

- To investigate whether Tenofovir alafenamide based regimens are less nephrotoxic than Tenofovir disoproxil based regimens.
- To evaluate whether Tenofovir alafenamide contained regimens could decrease less mineral bones compared to Tenofovir disoproxil contained regimens.
- To evaluate the efficacy of TAF in treating HIV/hepatitis co-infection

Methods

Criteria for considering studies for this review

Types of studies

We will include randomized control trials comparing tenofovir alafenamide to tenofovir disoproxil.

Types of participants

HIV-infected adult patients under TAF and TDF based regimens.

Types of interventions

TAF based regimens

Types of outcome measures

Primary outcomes

- serum clearance Creatinine,
- proteinuria,
- HBV DNA
- HBsAg
- HBeAg

Secondary outcomes

- bone mineral density,
- serum cholesterol,
- viral load,
- CD4 count
- Hepatic Transaminases
- Adverse events

Search methods for identification of studies

MeSH descriptor HIV Infections explode all trees

AND

MeSH descriptor HIV explode all trees

AND

hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human imminodeficiency virus OR human immune-deficiency virus OR human immuno-deficiency virus OR human immun* deficiency virus OR acquired immunodeficiency syndrome

AND

tenofovir OR TNF OR TDF OR PMPA OR Tenofovir Disoproxil OR Tenofovir Disoproxil Fumarate OR (Disoproxil Fumarate, Tenofovir) OR Fumarate, Tenofovir Disoproxil OR Viread

AND

Tenofovir alafenamide OR tenofovir prodrug OR TAF

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*)

Electronic searches

We will search the following electronic databases:

- CENTRAL (Cochrane Central Register of Controlled Trials)
- Scorpus
- Web of science
- LILACS
- PubMed
- CINAHL

Searching other resources

We will also search conference abstract archives on the web sites of 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).

Data collection and analysis

The methodology used for collecting and analyzing data will be based on the guidance of the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2011). Two Authors will work independently, reviewed the abstracts of all studies identified through database searches or other resources. Where there will have any question of eligibility, we will obtain the full text of the article for closer examination.

Selection of studies

Two authors (JT and LM) analyzed the studies obtained from the literature search for eligibility criteria. Titles and abstracts were independently screened to obtain full text of eligible studies. In the cases of any disagreement, the resolution was reached by consensus.

Data extraction and management

Two authors independently extracted data into a standardized, pre-tested data extraction form. The following

characteristics were extracted from each included study:

- Study details: trial identification number; author(s); published or unpublished; year of publication
- Study settings
- Study design
- Follow up: duration and completeness of follow up
- Study power
- Details of participants: age range; gender; CD4 count, viral load, HIV stage
- Details of treatment
- Outcomes: primary and secondary
- Risk of bias assessment

Assessment of risk of bias in included studies

The risk of bias will be assessed using the following domains:

• Sequence generation: how the allocation sequence was generated and whether it was adequate.

• Allocation concealment: how the allocation sequence was concealed and whether it was adequate.

• Blinding of participants, personnel, and outcome assessors.

• The description of the completeness of outcome data for each main outcome.

• Selective outcome reporting.

• Baseline characteristics for observational studies.

• Other potential sources of bias

Two reviewers will assess independently the risk of bias in different included study. Each domain will be graded as being at high, low, or moderate risk of bias.

Measures of treatment effect

When assessing outcome, for continuous outcomes (e.g. serum clearance creatinine, viral load) we will use mean differences, and for dichotomous outcomes (e.g. all causes of mortality) we will compare proportions using relative risks. In case where outcomes have been assessed several times, data for each specific time point will be extracted.

Unit of analysis issues

For trials with more than one - and very similar - control arms, the results for these arms will be combined in the meta-analysis. The same approach will be used for very similar treatment arms. If all arms in a multi-arm trial are to be included in the meta-analysis and one treatment arm is to be included more than once in some comparisons, then we will divide the number of events and the number of participants in that arm by the number of treatment comparisons made.

Dealing with missing data

If there is missing data among included studies, we will contact study authors to obtain data missing from published studies.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the included trials studies. If we find substantial heterogeneity (I^2 greater than 50%), we will investigate potential reasons for the heterogeneity.

Assessment of reporting biases

When assessing included studies, we will investigate incomplete reporting bias. In addition, we will strengthen our search strategy to find a range of databases and sources of grey literature and not restricting by language or publication status. Lastly, we will use funnel plots to assess publication bias when included studies are equal or greater than 10.

Data synthesis

If data from studies are as similar as possible, we will be combined in Cochrane's Review Manager Software (RevMan 2014) for meta-analysis for the different outcomes.

If data from studies are not sufficiently the same, the results will be summarized in a narrative manner. GRADE evidence profiles and summary of findings tables will be generated.

When interventions and study populations are sufficiently similar across the different studies, we will pool the data across studies and estimate summary effect sizes using both fixed- and random effects models.

Subgroup analysis and investigation of heterogeneity

The I^2 test of heterogeneity will be performed to ensure that the differences between the results of each trial could not be expected by chance.

If there is substantial statistical heterogeneity, subgroup analysis will be then conducted. Subgroups analysis will be performed by age, gender, baseline CD4 counts less and more than 150 cells/mm3 and different regimens.

Conclusion

This systematic review could widely impact on HIV treatment. In fact, TDF is the WHO first line regimen, largely used in middle and low income countries. Its nephrotoxicity and bone mineral density effects are restricted its uses. We will analysis whether TAF could be completely replaced by TDF. In addition, we will investigate the effect of TAF compared to TDF on HIV/Hepatitis co-infection.

Registration

The review was registered on Prospero: Tamuzi Lukenze Jacques, Olatunji Adetokunboh, Esperence Manuana, Andy Bulabula Hamama. Tenofovir alafenamide versus tenofovir disoproxil: systematic review and meta-analysis. PROSPERO 2016:CRD42016032717 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016032717

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