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# Using a single tablet regimen of darunavir, cobicistat, emcitabine, and tenofovir alafenamide in virally suppressed HIV-1 patients is an adequate treatment option for controlling HIV

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**ABSTRACT** A clinical decision report using:

Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV*. 2018;5(1):e23-e34. [https://doi.org/10.1016/S2352-3018\(17\)30179-0](https://doi.org/10.1016/S2352-3018(17)30179-0)

for a patient with virologically suppressed HIV-1.

**Keywords:** *darunavir, cobicistat, emcitabine, tenofovir alafenamide, HIV-1, virologically suppressed HIV*

## Clinical-Social Context

Barbara Jones (Pseudonym) is a 52-year-old woman who presented to the HIV clinic for a follow up appointment. Ms. Jones contracted HIV years ago due to IV drug use and has been taking her medications consistently every day. Ms. Jones had labs drawn prior to clinic which showed a CD4+ count of over 700 and a viral load of <30 copies per mL. Ms. Jones has been adherent with her medications but expressed frustration over taking medications every day. She states that she is simply tired of taking her medications. She is currently going through menopause associated with daily vasomotor symptoms, which is making her feel worse.

Ms. Jones has a very supportive family, as she and her husband have dealt with HIV together. They do not have any children and are financially stable at the moment. Ms. Jones has not used illicit drugs since her 20s and has never had a history of hepatitis B or C. Ms. Jones asked us whether there was a way to just stop taking medications altogether since her viral load has been so low for over a year now. We explained to her that she cannot stop taking her medications but could consider simplifying her regimen down to one single tablet. This prompted the team to discuss the use of a single tablet regimen in the treatment of HIV in a virally suppressed patient based on her current regimen.

PRIYA KATHURIA is a 4<sup>th</sup> year medical student at the Wayne State University School of Medicine.



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## Clinical Question

Is there a significant benefit to using a specific fixed-dose single tablet antiretroviral regimen over a multi-tablet regimen in patients with virally suppressed HIV-1?

## Research Article

Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV*. 2018;5(1):e23-e34. [https://doi.org/10.1016/S2352-3018\(17\)30179-0](https://doi.org/10.1016/S2352-3018(17)30179-0)<sup>1</sup>

## Description of Related Literature

The literature review was conducted on PubMed by searching for the key terms “HIV”, “single tablet”, and “drug regimen”. This yielded 401 results. The following filters were applied which yielded 37 results: randomized controlled trial, meta-analysis, publication date within last 5 years. Titles and abstracts were manually scanned through for relevant papers that directly compared a single tablet regimen to a multi tablet regimen. This yielded 9 results for review. An additional review was conducted on Google Scholar using the terms “HIV”, “single tablet”, and “regimen”, again looking at papers published in the last 5 years. This yielded 47 results. No additional articles were found for review.

Eron et al. conducted a phase 3 randomized international, multi-center, double-blinded study which looked at the efficacy of a single-tablet regimen containing darunavir, cobicistat, emtricitabine, tenofovir alafenamide compared to control of darunavir and cobicistat plus emtricitabine and tenofovir disoproxil fumarate.<sup>2</sup> Results of the study demonstrated that the single tablet regimen achieved superior viral suppression rates at 91.4% vs 88.4% in the control. Since a different study with larger sample size, and more analytic factors was found, this study was not included for appraisal.

Pozniak et al. conducted a 96 week, phase 3b, open-label, randomized study to look at the efficacy and safety of switching to a single tablet-regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate from an NNRTI based regimen.<sup>3</sup> Results of this study demonstrated the single tablet regimen to be safe and effective and reduced NNRTI-related neuropsychiatric symptoms. This study was not selected due to the base treatment being an NNRTI regimen. Our patient does not take NNRTI's as they are no longer commonly prescribed in the HIV clinic.

Rizzardini et al. conducted a randomized, open label study which compared an abacavir plus lamivudine treatment to a single tablet regimen of elvitegravir, cobicistat, tenofovir alafenamide.<sup>4</sup> Results of this study demonstrated the single tablet regimen to be noninferior to the control group and noted it to be efficacious and a well-tolerated option. Due to the low sample size and untraditional control group used that was not representative of our patient, this trial was excluded for appraisal.

Stellbrink et al. conducted a randomized, double-blinded multicenter trial comparing the single-tablet regimen consisting of bictegravir, emtricitabine, and tenofovir to dolutegravir co-formulated with emtricitabine and tenofovir.<sup>5</sup> Results of this study demonstrated non-inferiority of the bictegravir regimen group when compared to the dolutegravir regimen group. However, this study compared one single-tablet regimen to another co-formulated group, which did not align with our patient's current multi-drug regimen.

Arribas et al. conducted the STRAGETY-PI trial, a study examining the efficacy of switching from a multi-drug regimen consisting of ritonavir-boosted protease inhibitor co-formulated with emtricitabine and tenofovir to a single-tablet regimen consisting of elvitegravir, cobicistat, emtricitabine, and tenofovir.<sup>6</sup> Results of this study demonstrated that the single-tablet regimen was an effective treatment option for virologically suppressed HIV-1 infected individuals. This study was excluded for appraisal as it did not align with our patient's current drug regimen.

Clay et al. conducted a meta-analysis comparing outcomes of single and multi-tablet regimens in HIV.<sup>7</sup> Findings of this study demonstrated that there are preliminary findings showing advantages of the single-tablet regimens over multi-tablet for adherence,



low discontinuation rates, improvement in quality of life, cost-effectiveness, and viral suppression. Although this study demonstrates efficacy in single tablet regimens, it is a meta-analysis which is not appropriate for appraisal.

Orkin et al. ran the EMERALD trial: an international, multi-center, open-labeled, randomized controlled trial that took place in 106 centers in North America and Europe from April 2015 to February 2017.<sup>1</sup> Patients were randomized by computer into a study group that received darunavir, cobicistat, emtricitabine, and tenofovir alafenamide in a single fixed-dose tablet or control group with a normal multi-drug regimen. Primary endpoint of this study was at 48 weeks which looked at various factors such as viral load and CD4 count. It is important to note two additional studies that stemmed from the EMERALD trial: Huhn et al.<sup>8</sup> and Eron et al.<sup>9</sup> which assess various outcomes across different subgroups of patients. The EMERALD study was chosen for appraisal due to the large sample size, adequate randomization, and direct applicability to our patient in regard to her current drug regimen. This topic meets level A strength of recommendation regarding the SORT criteria.<sup>10</sup>

## Critical Appraisal

This study according to the SORT criteria carries Level 1 evidence.<sup>10</sup> This study EMERALD is a phase 3 international, multi-center, randomized controlled open-labeled trial.<sup>1</sup> This trial was conducted at 106 centers across 9 countries in North America and Europe. Patients 18 or older were enrolled if they had HIV-1 that was virologically suppressed, with at least one viral load less than 50 copies per mL within 2 months before screening. These patients had to demonstrate no history of failure on a darunavir-based regimen and absence of darunavir resistance mutations. The patient's medication plan prior to the study needed to consist of a boosted protease inhibitor in conjugation with tenofovir disoproxil fumarate and emtricitabine for at least 6 months prior to being screened. Patients GFR had to be at least 50 mL/min. Exclusion criteria included pregnant or breastfeeding women, patients with hepatitis B or C, patients with active malignancy or severe infection. It was unclear how patients were selected for this study, which makes us unable to determine if selection bias was present. No explanation was given as to how patients were recruited, so participation bias is unable to be determined.

The randomization process was conducted via a computer system where patients were assigned to either the study or control regimen in a 2:1 ratio.<sup>1</sup> It was unclear as to why more patients were in the study group versus control group. This was an open-label study, so investigators, patients, and sponsors knew which treatment was being assigned to the patients. There was no mention as to why this study was not conducted as a blinded study. The double blinding may not have been done because this would require all patients to take multiple pills as opposed to one tablet containing all the medications. Patients were treated for 48 weeks and were required to take their medications once per day with food. The study group received one tablet containing darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg.<sup>1</sup> The control group was provided medications as well, which ensured equality between the two groups.

Patients completed study visits at weeks 2, 4, 8, 12 and then every 12 weeks until the end of the study.<sup>1</sup> At visits, treatment adherence was documented by monitoring pill count. Other prescribed medications and any adverse events was documented as well. Labs at each visit consisted of testing for viral load, CD4 count, renal function, and other blood parameters. Patients had a urinalysis and urine chemistry done as well. Renal proteinuria and fasting metabolic lipid panel were collected during the study. Bone assessments and DXA scan was done as part of a sub-study at certain sites. Patients were randomly selected for this if they previously provided consent. DXA scans were done at weeks 24 and 48. Other bone biomarkers collected were alkaline phosphatase, collagen, parathyroid hormone, vitamin D. The ability to look at various factors gives the study greater credibility as they are looking at various side effects and changes that can occur as patients take these HIV medications.

1299 patients were screened for the trial, 1141 underwent randomization and were included. 763 were assigned to study group, 378 to control.<sup>1</sup> Of this, 1087 patients were included in an intention-to-treat analysis at 48 weeks. During treatment, 34 patients discontinued from the study group, 20 from the control group. These discontinuations were due to loss to follow up, withdrawn consent, and adverse events. Baseline characteristics were matched between the two groups to eliminate any potential confounding bias. When looking at Table 1 which showed demographics of patients, Ms. Jones characteristics matched up well with other patients that were selected for the trial.

Virological response was seen in 94.9% of the study group and 93.7% in the control group as both had viral load <50 copies per mL.<sup>1</sup> Based on this, NNT/NNH was calculated at 83.3, where this many patients would have to receive the study treatment for one



additional patient to not have the study outcome. No mutations or resistance was noted to darunavir, tenofovir, or emtricitabine. Low virologic rebound rates were seen which was quantified as >50 copies per mL in both groups. Adherence measured by pill count was 99.7% in the study group and 99.3% in the control. Safety profiles were similar between the two groups. The most common adverse events noted was URI, diarrhea, nasopharyngitis, with the study group having slightly higher incidence of adverse effects. Renal adverse events were present in 4% of the study group and 5% of the control. Measurements in lipid panels were similar in both groups. The study regimen showed improvements in proteinuria in comparison to the control, but GFR was preserved in both. A bone investigation sub-study demonstrated increased bone mineral density at hip, lumbar spine, and femoral neck in study group in compared to control. There was less bone turnover, which was attributed to using tenofovir alafenamide over tenofovir disoproxil fumarate. Overall, the new regimen combines the known efficacy of darunavir, decreased resistance, and safety advantages of tenofovir alafenamide into one single-tablet regimen. This is a feasible regimen that can be put into practice.

This study was sponsored and funded by Janssen.<sup>1</sup> The funder had access and was involved in all aspects of study design and conduction, data collection and analysis. This trial was registered with ClinicalTrials.gov.

## Clinical Application

After discussion with Ms. Jones that we could use one single tablet that combines all 3 of her medications into one pill, Ms. Jones was accepting of this plan. This one pill would simplify her regimen and provide adequate treatment to treat her HIV as she is already virally suppressed and adherent with her medications. Ms. Jones does not have many co-morbid conditions, so no adjustments in dosing would need to be done. As she gets older, she will be at higher risk for osteoporosis. We explained how using this regimen would be beneficial to her, as improvements in osteoporotic changes were seen based on the study results. Although there was not much of a difference in efficacy between the two groups, this regimen will simplify Ms. Jones medication routine as wished for.

The potential harms to this treatment are minimal as Ms. Jones has not experienced any serious adverse effects with her current medication routine. We expressed to her that she may still experience diarrhea, headaches, or upper respiratory infections, but this would not be any different from her current routine. Her kidney function has always been stable, so there were no concerns for worsening function. She agreed to switch her regimen to this fixed-dose single tablet regimen, and we would follow up with her in one month to assess how she is doing.

## New Knowledge Related to Clinical Decision Science

By using the research found, we were able to better Ms. Jones life by simplifying her medication routine. HIV patients have to be consistent and adhere to their regimen in order to live a relatively normal life. Since the study demonstrated that the regimen is effective without much harm, we decided to use it see how she responds to the new treatment. This may benefit other HIV patients in the clinic, especially those with poor adherence who struggle to take multiple pills every day. In fact, when starting a patient on an HIV regimen, this may be advantageous and should be considered when making treatment decisions. This application of clinical research affirms why it is important to stay up to date on new treatments, especially in a field like HIV where there are hundreds of drug combinations to choose from. It is also important to understand the patient's wishes and frustrations and use those to guide our decision making.

## Conflict Of Interest Statement

The author reports no Conflict of Interest with any pharmaceutical mentioned in this manuscript.

## References

1. Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV.* 2018;5(1):e23-e34. [https://doi.org/10.1016/S2352-3018\(17\)30179-0](https://doi.org/10.1016/S2352-3018(17)30179-0)

2. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS*. 2018;32(11):1431-1442. <https://doi.org/10.1097/QAD.0000000000001817>
3. Pozniak A, Flamm J, Antinori A, et al. Switching to the single-tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir DF from non-nucleoside reverse transcriptase inhibitor plus coformulated emtricitabine and tenofovir DF regimens: Week 96 results of STRATEGY-NNRTI. *HIV Clin Trials*. 2017;18(4):141-148. <https://doi.org/10.1080/15284336.2017.1338844>
4. Rizzardini G, Gori A, Miralles C, et al. Randomized study evaluating the efficacy and safety of switching from an abacavir/lamivudine-based regimen to an elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen. *AIDS*. 2019;33(10):1583-1593. <https://doi.org/10.1097/QAD.0000000000002244>
5. Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e364-e372. [https://doi.org/10.1016/S2352-3018\(19\)30080-3](https://doi.org/10.1016/S2352-3018(19)30080-3)
6. Arribas JR, DeJesus E, van Lunzen J, et al. Simplification to single-tablet regimen of elvitegravir, cobicistat, emtricitabine, tenofovir DF from multi-tablet ritonavir-boosted protease inhibitor plus coformulated emtricitabine and tenofovir DF regimens: week 96 results of STRATEGY-PI [published correction appears in *HIV Clin Trials*. 2018 Aug;19(4):163]. *HIV Clin Trials*. 2017;18(3):118-125. <https://doi.org/10.1080/15284336.2017.1330440>
7. Clay PG, Yuet WC, Moecklinghoff CH, et al. A meta-analysis comparing 48-week treatment outcomes of single and multi-tablet antiretroviral regimens for the treatment of people living with HIV. *AIDS Res Ther*. 2018;15(1):17. Published 2018 Oct 30. <https://doi.org/10.1186/s12981-018-0204-0>
8. Huhn GD, Eron JJ, Girard PM, et al. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-experienced, virologically suppressed patients with HIV-1: subgroup analyses of the phase 3 EMERALD study. *AIDS Res Ther*. 2019;16(1):23. Published 2019 Aug 29. <https://doi.org/10.1186/s12981-019-0235-1>
9. Eron JJ, Orkin C, Cunningham D, et al. Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment-experienced, virologically-suppressed adults living with HIV-1. *Antiviral Res*. 2019;170:104543. <https://doi.org/10.1016/j.antiviral.2019.104543>
10. Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, Bowman M. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004 Jan-Feb;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>

