Pharmacokinetics (PK) of Bictegravir (BIC) in Combination with Polyvalent Cation Containing (PVCC) Antacids and Supplements

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Background

- Polypharmacy is more common in People living with HIV than the general population\(^1\)

- Polyvalent cations (PVCs) may be used as antacids or supplements from both physician prescribed and OTC products or supplements
  - May include Magnesium, Aluminium, Iron (Ferrous) and Calcium

- PVCs may cause DDIs primarily through chelation with other drugs
  - Formation of insoluble complexes leading to impaired drug absorption

- INSTIs as a class are susceptible to DDIs with PVC primarily through chelation\(^2-10\)

DDI, drug drug interactions; INSTI, integrase strand transfer inhibitors; OTC, over the counter
Bictegravir (BIC; B) is an un-boosted integrase strand transfer inhibitor (INSTI) with a high barrier to resistance

- Co-formulated with emtricitabine (F) and tenofovir alafenamide (TAF) into a single-tablet regimen (B/F/TAF)
  - BIC has demonstrated a wide therapeutic window\(^2\)
  - BIC also susceptible to interaction with PVC\(^3\)

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Primary Objective

- Evaluate the effect of administration of aluminum/magnesium (Al/Mg) antacids and of calcium (Ca) or iron (Fe) supplements with B/F/TAF fixed-dose combination (FDC) on BIC pharmacokinetics (PK)
  - Can this potential effect be mitigated by food?
  - Can this potential effect be mitigated by staggered administration?

Secondary Objective

- Evaluate the safety and tolerability of B/F/TAF when given alone or in combination with Al/Mg antacids and Ca or Fe supplements
Methods: Study Design and Participant Cohorts

### Phase 1, open-label, single-dose, fixed-sequence, multiple-cohort, multiple-period study in healthy participants

<table>
<thead>
<tr>
<th>Healthy Subjects</th>
<th>Intensive PK sampling</th>
<th>Day 1</th>
<th>2–8</th>
<th>9</th>
<th>10–16</th>
<th>17</th>
<th>18–24</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1: Simultaneous Fasted, n=14</td>
<td>B/F/TAF Fasted (reference)</td>
<td>Washout</td>
<td>B/F/TAF + Al/Mg</td>
<td>Washout</td>
<td>B/F/TAF + Ca</td>
<td>Washout</td>
<td>B/F/TAF + Fe</td>
<td></td>
</tr>
<tr>
<td>Cohort 2: Simultaneous Fed, n=14</td>
<td>B/F/TAF Fasted (reference)</td>
<td>Washout</td>
<td>B/F/TAF + Al/Mg</td>
<td>Washout</td>
<td>B/F/TAF + Ca</td>
<td>Washout</td>
<td>B/F/TAF + Fe</td>
<td></td>
</tr>
<tr>
<td>Cohort 3: Staggered Fasted, n=14</td>
<td>B/F/TAF Fasted (reference)</td>
<td>Washout</td>
<td>B/F/TAF 2 h before Al/Mg</td>
<td>Washout</td>
<td>B/F/TAF 2 h after Al/Mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 42 participants were enrolled
- All treatments were administered as single doses
- PVCC antacids and supplements tested were:
  - Antacid (aluminum hydroxide 1600mg, magnesium hydroxide 1600mg, simethicone 160mg)
  - Calcium carbonate (1200mg) supplement
  - Ferrous-fumarate (324mg) supplement

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Methods – Safety and PK Analyses

Pharmacokinetic Analyses

- PK parameters (mean [%CV]) include
  - Area Under the Curve (AUC∞ [h·ng/mL]),
  - Maximal concentration (Cmax [ng/mL])
  - Concentration 24 hours post-dose (C24 [ng/mL])
  - Projected Inhibitory Quotient (IQ)

- BIC exposures from test treatments were compared with the reference treatment as geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals.

- The lack of drug-drug interaction boundary was 70% to 143%

Safety

- Adverse event (AE) monitoring, clinical laboratory assessments and physical examinations were performed throughout the study and follow-up
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 Fasted, Simultaneous n=14</th>
<th>Cohort 2 Fed, Simultaneous n=14</th>
<th>Cohort 3 Fasted, staggered n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>32 (25–41)</td>
<td>41 (27–45)</td>
<td>29 (22–43)</td>
</tr>
<tr>
<td>Female, %</td>
<td>29</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Median BMI, kg/m² (range)</td>
<td>26 (22–30)</td>
<td>28 (25–30)</td>
<td>26 (22–29)</td>
</tr>
<tr>
<td>Median eGFR&lt;sub&gt;CG&lt;/sub&gt;, mL.min (range)</td>
<td>119 (98–168)</td>
<td>117 (91–161)</td>
<td>129 (98–152)</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African-American</td>
<td>43</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>White</td>
<td>57</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>57</td>
<td>64</td>
<td>86</td>
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BMI, body mass index; eGFR<sub>CG</sub>, estimated glomerular filtration rate (Cockcroft-Gault).
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Results – Safety and Tolerability

- All treatments were generally well tolerated
- 41/42 participants completed the study
  - 1 discontinuation due to Grade 2 urticaria which resolved on day 7
  - All AEs were Grade 1 or 2 in severity
  - Constipation observed was thought to be associated with use of antacids/Ca supplements
  - There were no clinically significant changes from pre-dose in median values for haematology or clinical chemistry parameters for any treatment
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fasted

BIC PK Parameter, Mean (%CV)  Test n=14  B/F/TAF Alone, Fasted (reference) n=14  % GLSM Ratio (90% CI)

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Al/Mg, B/F/TAF administered fasted with Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Ca, B/F/TAF administered fasted with Ca supplement; Fe, B/F/TAF administered fasted with Fe supplement.
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fasted

![Graph showing BIC concentration over time for different conditions.](image)

**BIC PK Parameter, Mean (%CV)**

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<tr>
<td>B/F/TAF fasted + Al/Mg antacid (test)</td>
<td>AUC∞, h·μg/mL</td>
<td>28.0 (52.5)</td>
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Al/Mg, B/F/TAF administered fasted with Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Ca, B/F/TAF administered fasted with Ca supplement; Fe, B/F/TAF administered fasted with Fe supplement

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Effects of PVCC Antacids and Supplements on BIC Exposure
Simultaneously, Fasted

BIC PK Parameter, Mean (%CV) | Test n=14 | B/F/TAF Alone, Fasted (reference) n=14 | % GLSM Ratio (90% CI)
--- | --- | --- | ---
B/F/TAF fasted + Al/Mg antacid (test) | AUC$_{\infty}$, h·μg/mL 28.0 (52.5) | 122 (24.4) | 21.2 (17.6, 25.7)
B/F/TAF fasted + Ca supplement (test) | AUC$_{\infty}$, h·μg/mL 85.0 (43.1) | 122 (24.4) | 66.7 (56.7, 78.4)
Effects of PVCC Antacids and Supplements on BIC Exposure
Simultaneously, Fasted

Simultaneous fasted co-administration of B/F/TAF with Al/Mg and Fe-containing antacids/supplements is not recommended
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fed

*n=14 for test treatment. Al/Mg, fed, B/F/TAF administered fed with Al/Mg antacid; Alone, fasted, B/F/TAF administered fasted alone; Ca, fed, B/F/TAF administered fed with Ca supplement; Fe, fed, B/F/TAF administered fed with Fe supplement.

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Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fed

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<td>B/F/TAF fed + Al/Mg antacid (test)</td>
<td>AUC$_{\infty}$, h·µg/mL</td>
<td>50.8 (34.8)</td>
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*n=13 for test treatment. Al/Mg, fed, B/F/TAF administered fed with Al/Mg antacid; Alone, fasted, B/F/TAF administered fasted alone; Ca, fed, B/F/TAF administered fed with Ca supplement; Fe, fed, B/F/TAF administered fed with Fe supplement.

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Effects of PVCC Antacids and Supplements on BIC Exposure
Simultaneously, Fed

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Effects of PVCC Antacids and Supplements on BIC Exposure
Simultaneously, Fed

Administration of food with B/F/TAF and Ca or Fe supplements mitigated chelating effect of PVCs

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<td>B/F/TAF fed + Fe supplement (test)</td>
<td>AUC$_\infty$, µg/mL</td>
<td>77.3 (24.8)</td>
<td>93.7 (27.2)</td>
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*n=13 for test treatment, Al/Mg, fed, B/F/TAF administered fed with Al/Mg antacid; Alone, fasted, B/F/TAF administered fasted alone; Ca, fed, B/F/TAF administered fed with Ca supplement; Fe, fed, B/F/TAF administered fed with Fe supplement.
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Effect of Al/Mg Antacids on BIC Exposure
Staggered, Fasted

After, B/F/TAF administered fasted 2 h after Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Before, B/F/TAF administered fasted 2 h before Al/Mg antacid.
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Effect of Al/Mg Antacids on BIC Exposure
Staggered, Fasted

Staggering of B/F/TAF 2 h before and 2 h after Al/Mg antacid administration resulted in modest decreases in BIC AUCₜₐₜ (23% and 52%, respectively)

Separation of B/F/TAF dose by ± 2 hours attenuated the chelating effect of PVCC antacids/supplements

After, B/F/TAF administered fasted 2 h after Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Before, B/F/TAF administered fasted 2 h before Al/Mg antacid.

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Effect of Al/Mg Antacids on BIC Exposure
Staggered, Fasted

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After, B/F/TAF administered fasted 2 h after Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Before, B/F/TAF administered fasted 2 h before Al/Mg antacid.

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The number of times BIC $C_{\text{tau}}$ (2.61 mcg/mL) is above the BIC $\text{paEC}_{95}$ (0.162 mcg/mL)

A high mean inhibitory quotient (IQ) of 16.1* was observed for BIC in the registration Phase 3 studies of B/F/TAF (N=584)

*Mathias A et al. ACCP Global Conference on Clinical Pharmacy 2018 #TueAM-58
Kabagambe et al. BHIVA 2019, O08
Summary of BIC C\textsubscript{24} Changes After Various PVCC Antacid/Supplement Co-administration Conditions\textsuperscript{*}

The effects on BIC PK and IQ were limited when PVCC antacids/supplements were administered either simultaneously with B/F/TAF under fed conditions or staggered from B/F/TAF administration by \( \pm 2 \) h under fasted conditions.

- Both coadministration conditions are expected to yield BIC IQ values within the therapeutic window for HIV-1–infected patients, as previously defined\textsuperscript{1}

\textsuperscript{*}IQ calculated via product of BIC AUC GLSM ratio and mean BIC IQ from B/F/TAF registrational trials (IQ 16.1); green and grey shaded areas denote BIC IQ within and outside of, respectively, BIC therapeutic window, as previously defined.\textsuperscript{11}

\textsuperscript{1} Lutz JD, et al. International Workshop on Clinical Pharmacology of Antiviral Therapy 2018, poster 6. Kabagambe, BHIVA, 2019, 008
The analysis suggested that if all patients in the Phase 3 registrational studies were administered B/F/TAF 2 h after Al/Mg antacids, mean BIC IQ (%CV) is predicted to be 7.6 (44%).

*Mean IQ (%CV) in Phase 3 registrational studies was 16.1 (33%); BIC C_{24} GLSM ratio was 0.47 and test C_{24} %CV was 44% when B/F/TAF was administered fasted 2 h after Al/Mg antacid.

Kabagambe et al. BHIVA 2019, O08
Conclusions

- Decreased BIC exposure from chelation by PVCC antacids/supplements can be attenuated by staggering administration ± 2 hours and/or administering with food.

- Mean IQ of 7.6 is predicted in HIV-1–infected patients co-administering B/F/TAF in a fasted state 2h after PVCC antacid/supplement therapy.
  - Reduction in BIC exposure (IQ <1) is unlikely.

- European B/F/TAF SmPC recommendations:\n  - Al/Mg: B/F/TAF should be administered at least 2 hours before, or with food 2 hours after antacids containing Al or Mg.
  - Iron: Take B/F/TAF at least 2 hours before iron supplements, or take together with food.
  - Calcium: Can be taken together, without regard to food.

1. Bictegravir/emtricitabine/tenofovir alafenamide SmPC via medicines.org.uk accessed 30/3/19
Kabagambe et al. BHIVA 2019, O08
Acknowledgments

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