

# Exploring flow synthesis as a method for local and economically-viable ARV manufacture

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## 01. Introduction

- **High demand** for antiretrovirals (ARVs) in Sub-Saharan Africa<sup>1</sup>
- Active pharmaceutical ingredients (APIs) account for **~80% of ARV costs**<sup>2</sup>
- South Africa imports **100 % of APIs** worth **~\$800 million** annually<sup>2</sup>
- **Local API** manufacturing could:
  - *Secure supply chains*
  - *Reduce costs*
  - *Accelerate the introduction of new treatments*
  - *Expand HIV prevention programs*

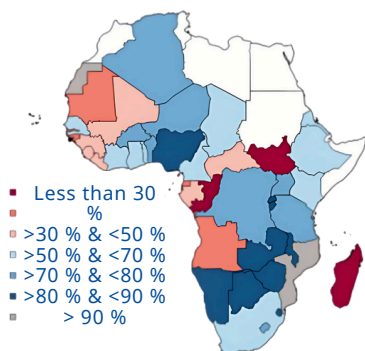


Figure 1: Percentage of people on ARVs in Africa, 2021<sup>2</sup>

- **Batch chemistry** is the **standard** method for **drug synthesis**, but **continuous flow synthesis**, such as for lamivudine, is a **viable alternative** (Fig. 2).

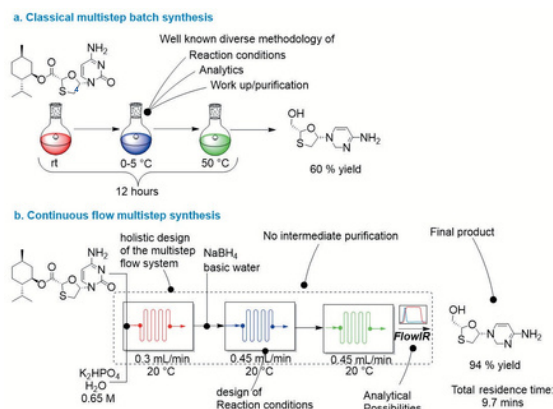


Figure 2: Comparison between batch and continuous flow API synthesis<sup>4,5</sup>

## 02. Objective

In this project, we seek to **employ continuous flow synthesis to develop cost-effective, greener processes for the manufacture of selected ARVs** relevant to South Africa

## 03. Methodology

- Batch synthesis of the ARV drugs below (Fig. 3). LC-MS and NMR were used for characterisation of the intermediates and final drugs.
- Translated the batch to continuous flow for improved efficiency and scalability.
- The **Synthetron Reactor** (Fig. 4) was chosen for its unique advantages:

- its **compact size**,
- **versatility in reaction conditions**,
- **cost savings** from higher concentrations,
- the **innovative spinning disk** that enhances mixing.<sup>5, 6</sup>



Figure 4: Synthetron continuous flow reactor

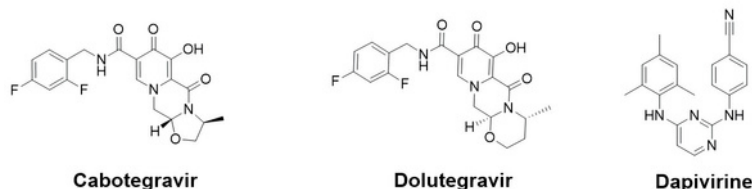


Figure 3: API structures of the ARV drugs under development in continuous flow

## 04. Discussion

### Synthetic Route Adjustments:

- Created a cost-effective common intermediate for cabotegravir and dolutegravir by removing expensive reagents.
- Validated a new synthetic route for all three APIs using batch chemistry.

### Flow Chemistry Optimisation:

- Enhanced cabotegravir/dolutegravir synthesis in flow, achieving 100 % conversion to key intermediates.
- Established a greener, more cost-effective method.
- Increased throughput.

### Cost of Goods Model:

- Developed a real-time monitoring model for manufacturing costs, improving financial management.

## 05. Conclusion

- ARV API **continuous flow** synthesis provides:
    - *increased efficiency*,
    - *scalability*,
    - *and cost reductions*.
  - **Local API production** is vital for:
    - *securing supply chains and*
    - *reducing import reliance*.
  - This approach is **essential** for meeting Africa's ARV demand and expanding **access to HIV treatments**. The **next phase** of the project involves:
    - *finalising*
    - *flow optimisation and*
    - *transferring the technology to CPT Pharma*
- for proof-of-concept testing at kg scale.

## 06. Related literature

1. Fact sheet 2024 - Latest global and regional HIV statistics on the status of the AIDS epidemic, *UNAIDS 2024*
2. The Department of Trade, Industry and Competition (DTIC) Annual Report **2022/23**
3. Thomas R. et al., *Lancet Glob Health*, Volume 9, Issue 5, **2021**
4. Mandala, D. et al., *Organic & Biomolecular Chemistry*, Volume 15, Issue 16, **2017**
5. Ramshaw C. et al., US Patents 7,125,527, **2006**
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## 07. Acknowledgements



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