Generating clinical evidence to improve HIV treatment

OPTIMIZE – a global partnership to accelerate access to simpler, safer and more affordable HIV treatment – supports clinical trials to rapidly fill in evidence gaps on new antiretroviral (ARV) drugs and formulations needed to inform global and national guidelines and improve HIV treatment options for patients and programs.

Current reality

The Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets and World Health Organization (WHO) "Treat All" guidelines require a rapid expansion of access to antiretroviral therapy (ART). Past clinical trial investments have resulted in increasingly simpler, more durable and less toxic treatment options.

<table>
<thead>
<tr>
<th>Year</th>
<th>Therapy</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Monotherapy, multiple times per day</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Triple therapy, twice daily</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Triple therapy, once-a-day</td>
<td></td>
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<tr>
<td>2019</td>
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Illustrative, actual doses vary by regimen.

New developments in the ART optimization effort have led to key clinical trials that will provide the necessary evidence to make further improvements to the safety, efficacy and affordability of ARVs.

How will new clinical evidence improve HIV treatment options?

Clinical trials close evidence gaps, inform guidelines, and result in streamlined drug delivery, including to adolescents, pregnant women, and people co-infected with tuberculosis.

- Reduced quantities of the Active Pharmaceutical Ingredients: lower doses and potentially smaller tablet size and better patient adherence
- Increased tolerability, lower toxicity and fewer side effects: improved adherence and lower rates of treatment failure and drug resistance treatment failure
- Earlier and higher rates of sustained viral suppression: decreased HIV transmission and incidence
- Reduced regimen discontinuation: decreased treatment failure

Key gaps in evidence – such as the effectiveness of new ARVs for HIV and tuberculosis co-infected or pregnant patients – must be filled in order to safely and effectively introduce next generation ART in the highest HIV burden countries.

To generate this evidence, well-run clinical trials that can inform expedited global and national guidance and facilitate regulatory approvals of quality generic ARVs are critical.

Aligning clinical trial efforts on a prioritized set of optimized ARVs also encourages competitive, sustainable and healthy markets. When multiple generic manufacturers invest in production of new regimens, patients and programs benefit from lower costs and a diversified supply chain that can prevent stockouts and improve quality of care.
Through ART optimization, powerful new drugs can bring in an era of exciting possibilities for making treatment simpler for patients to take and easier for healthcare workers to manage. New and existing treatment options present promising opportunities to transform treatment to reach the goal of ART optimization, especially first-line ART. More durable first-line ART would reduce the need for patients to transition to more expensive second-line ART.

Which ARV drugs and formulations have the most promise to transform HIV treatment?

Dolutegravir (DTG)
The availability of the first affordable, generic, single-pill HIV treatment containing DTG (known as TLD, co-formulated with tenofovir disoproxil fumarate, or TDF) is poised to transform HIV first-line treatment in low- and middle-income countries. TLD’s benefits include a rapid rate of viral suppression, a high barrier to resistance and low rates of side effects. DTG-based combinations also have the potential to play a role in second-line treatment.

Tenofovir Alafenamide Fumarate (TAF)
A generic, single-pill HIV treatment containing DTG and TAF could provide an alternative to TLD with similar antiviral efficacy and a smaller dose. TAF is substantially cheaper than TDF, a major cost driver of first-line therapy, and provides bone and renal toxicity benefits for the majority of patients.

Efavirenz (EFV)
A lower dose – decreasing from the current 600mg standard of care to 400mg – is as effective with the potential for lower risks of EFV-related side effects. Enabling access to a lower-dose EFV regimen provides a safe, effective and affordable alternative to DTG-based regimens.

Darunavir (DRV)
Efforts are underway to accelerate DRV’s availability by decreasing its cost, and enabling a lower-dose, single-pill formulation (boosted with ritonavir). Lower-dose DRV is as effective with the potential for lower risks of DRV-related side effects. DRV’s favorable efficacy and tolerability presents opportunities to optimize second-line treatment, either as an alternative to the boosted protease inhibitors atazanavir/ritonavir (ATZ/r) and lopinavir/ritonavir (LPV/r) or in combination with DTG.

How can the outcomes of these clinical trials save on the cost of HIV treatment?

A spotlight on South Africa demonstrates the potential impact of adopting an optimized generic, single-pill HIV treatment containing DTG and TAF.

- South Africa has the largest ART program in the world
- South Africa has over 42 million people on treatment
- South Africa consumes a quarter of the global ARV production
- From 2019 through 2023, through the adoption of an optimized generic, single-pill HIV treatment containing DTG and TAF, South Africa could save over 200 million U.S. dollars
- These savings would allow South Africa to treat an additional two million people with its current budget for ARVs

Conclusion

OPTIMIZE supports clinical trials of promising ARVs to fill critical gaps in research - accelerating access to simpler, safer and more affordable ART for all people living with HIV in low- and middle-income countries.

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