Insulin for All

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Declaration of interest

This work is financed by Health Action International (HAI).
The author does not have, and never had, any financial or other relation with the pharmaceutical industry.
The Addressing the Challenges and Constraints of Insulin Sources and Supply (ACCISS study) was started in 2015

- Phase 1 (2015-2018): Comprehensive evidence-base of the global insulin market, creating innovative policies, tools and interventions in the ACCISS toolkit
  - Price of insulin (cost of production, procurement prices, insulin map)
  - Selection (value of insulin, biosimilars, interchangeability, use)
  - Health systems (managing diabetes, cost of care, donations)
- Phase 2 (2018-2021): Using and testing the toolkit in Kyrgyzstan, Mali, Peru and Tanzania; intensive collaboration with WHO
Basic data on diabetes

- Global diabetes incidence is rapidly increasing (from 4.7% in 1980 to 8.5% of adults in 2014); becomes one of the major NCDs
- Diabetes Type 1 (DM1): no functioning pancreas, onset usually 10-16 years, fully insulin dependent
- Diabetes Type 2 (DM2): insulin resistance, partially linked to lifestyle. Most persons are on oral treatment, benefit from weight loss and diet; 10-15% must use insulin
- In most countries 90% DM-2 against 10% DM-1
Why are there so few adults with DM-1 in Africa?

Rural clinic in Uganda, 2017
Why are there so few adults with DM-1 in Africa?

Rural clinic in Uganda, 2017
“I wish I had AIDS”

person with type-1 diabetes, Cambodia

Insulin was discovered in 1921 and first used in 1922; and yet about 1 in 2 diabetes patients world-wide cannot afford and/or access this life-saving medicine.

There is international solidarity for the treatment of HIV/AIDS and other communicable diseases, but very little for NCDs, e.g. diabetes and cancer. Only recently Norway announced an international development programme focusing on NCDs.

Insulin is unstable; needs a cold-chain and 1-2 daily injections, plus blood glucose monitoring with strips.

In Tanzania, the cost of insulin, syringes and glucose monitoring for one child with diabetes-1 consumes 53% of the family income.
Basic data on insulin

- Novo Nordisk, Eli Lilly and Sanofi produce 92-95% of all insulin consumed in the world; their monopoly position leaves little room for competition and allows for high prices.

- Animal insulin has largely been replaced by recombinant “human” insulin. In HIC and MIC human insulin is aggressively being replaced by insulin “analogues.”

- Analogues are 5-10x as expensive as human insulin; insulin delivered in pens/cartridges is more expensive than in vials.
Changes in insulin sales, 1999-2009

(\textcolor{red}{\textit{red}}: human; \textcolor{blue}{\textit{blue}}: analogue; \textcolor{green}{\textit{green}}: animal)

High Income

Upper Middle Income

Lower Middle Income

Low Income

Beran et al. 2016
Median insulin prices in four Eurasian countries, 2019
10ml 100IU/ml in USD (public procurement, any presentation or brand)
<table>
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<tr>
<th></th>
<th>Year</th>
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</tr>
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<tbody>
<tr>
<td>Cochrane</td>
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Clinical evaluations of analogue insulin (Cochrane, WHO)

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Clinical advantages of analogue insulin in LMIC? (ACCISS Study)

- ACCISS: Systematic review of 21 cost-effectiveness studies comparing human insulin with insulin analogues; very few studies from LMIC
- 19 studies funded by industry: all conclude that analogues are clinically better and more cost-effective
- 2 independent studies, from Canada and Thailand: both conclude that insulin analogues offer no significant clinical benefit but are much more expensive, so not cost-effective
- ACCISS has just commissioned a full Cochrane systematic review on the cost-benefits of long-acting analogues
Estimated production cost; public prices in 13 LMIC
Production costs of analogues are comparable to human insulin

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<th>Human Insulin</th>
<th>Analogue Insulin</th>
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<tbody>
<tr>
<td></td>
<td>Cost of production</td>
<td>Government procurement price</td>
</tr>
<tr>
<td>Minimum</td>
<td>$2.28</td>
<td>$1.45</td>
</tr>
<tr>
<td>Maximum</td>
<td>$3.42</td>
<td>$25.21</td>
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<tr>
<td>Median</td>
<td>$5.30</td>
<td>$9.57</td>
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Source: Gotham et al 2018, Ewen et al 2019
Patent protection for several insulin analogues expired in 2014.

Yet new patents have been registered on delivery devices.
Biologic medicines

Proteins derived from cell culture / fermentation processes with bacteria or yeast, produced in living organisms

Examples: recombinant human & analogue insulins, cytokines, monoclonal antibodies, erythropoietin
Biosimilar insulins

A biosimilar insulin is similar to an existing insulin but cannot be considered identical because of the different manufacturing processes (different cell lines, protein sources, purification techniques).

Published studies have shown that biosimilars have comparable safety and clinical efficacy as the reference product:

- all PK and/or PD studies showed comparable parameters within pre-specified equivalence margins
- clinical studies: similar clinical efficacy and immunogenicity
- adverse events were similar between groups across studies

Source: https://doi.org/10.1371/journal.pone.0195012
### Categories of insulin manufacturers

#### Current market landscape (indicative list):
- at least 10 independent biosimilar manufacturers worldwide

<table>
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<th><strong>A. Insulin manufacturers controlling full manufacturing process</strong></th>
<th><strong>B. Manufacturers of finished product(s) only</strong></th>
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<td><strong>Originator insulin manufacturers</strong></td>
<td><strong>With crystals from Novo Nordisk, Lilly and Sanofi (unknown type of partnership)</strong></td>
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<tr>
<td>Denmark (Novo Nordisk), France (Sanofi), USA (Eli Lilly)</td>
<td>Belarus, India</td>
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<td><strong>Biosimilar insulin manufacturers with in-house insulins (crystal &amp; finished product) on the market</strong></td>
<td><strong>With crystals from biosimilar insulin manufacturers</strong></td>
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<td>India, China, UAE, Poland, Russian Federation (3), Ukraine (2), USA</td>
<td>Bangladesh, Brazil, China, India, Mexico, Morocco, Poland</td>
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Regulatory frameworks

- 2005: EMA first guideline on regulation of biosimilars
- 2006: First biosimilar registered in the European Union (EU)
- 2009: WHO first guideline on regulation of biosimilars
- 2014: EMA grants 1st market authorisation for a biosimilar insulin
- 2015: EMA first regulatory authority to develop insulin-specific guidelines; these have been adopted by many countries for the assessment of biosimilar insulins
- 2019: Revised WHO guidelines in preparation
Key point: need for clinical studies?

Over time, based on clinical experience, approval requirements through the biosimilar pathway for insulins could be simpler than those for a number of other (larger, more complex) recombinant proteins.

If the quality attributes of the biosimilar insulin are highly comparable to the reference product, the non-clinical and clinical data can be limited to pharmacokinetic (PK), pharmacodynamics (PD), and immunogenicity studies

=>no interchangeability challenges
Bio-similar insulins & prices

*Source: ACCISS report, Insulin price report, 2016 – UK Medicine information*

- Cost reductions at market launch for bio-similars (20-30%) are more modest compared to small molecule generic medicines
- In the USA and EU, the price of originator brands have decreased 12-51% once a biosimilar is introduced
- Opportunities of price reduction for human insulins:
  - 2019: Biocon Biologics offers human insulin to LMIC at US$ 2.50 for a 10ml vial (compared to cheapest US$ 3-4 from originators)
- Opportunities of price reduction for analogue insulins:
  - 2015: EMA and FDA approve Eli Lilly’s bio-similar glargine Basaglar®. In the UK, this is 15% below originator Sanofi’s Lantus®
Opportunities for rapid regulatory uptake of bio-similar insulin

- Biosimilar analogue insulins registered EU, Australia, Japan, USA
- WHO Prequalification programme pilot project started in 2017 with two cancer monoclonal antibodies (reference products & biosimilars); 14 Nov 2019 WHO announced inclusion of human insulin
- On-going WHO regulatory strengthening on the assessment of biotherapeutic medicines
  - Discussions to expand this work to Regional Regulatory Harmonisation initiatives (East African Community, West African Medicines Regulatory Harmonisation, EurAsianEU, etc)
Real or perceived problems with bio-similar insulins

- In Mali, a biosimilar from Morocco was later produced with an API from another country, with allegations of loss of potency.

- In Moldova, large quantities of biosimilar insulin had to be recalled because of bad quality and (perceived) lack of potency; there may also have been problems with ill-calibrated pens; and a lack of clinical guidance on switching between insulins.

- In Tanzania, public procurement of human insulin (Novo) has switched to biosimilar insulin. However, some doctors and patients have informally reported perceived lower potency. TFDA is studying the issue.
Suggested way forward towards insulin for all (1)

WHO:
- Prequalification of human insulin (originator and biosimilar)
- Support the development and market uptake of biosimilars (develop regulatory standards for biosimilar insulin; facilitate biosimilar registration at country level through joint assessments)

UNICEF/UNDP:
- Not-for-profit pooled insulin procurement facility for governments and public health systems

Governments in LMIC:
- Promote inclusion of insulin in public health insurance, part of UHC
- Educate prescribers and patients in cost-effective diagnosis and treatment of insulin-dependent diabetes; support patients
- Increase competition by promoting quality-assured biosimilars (initial focus on human insulin, until price of analogues is comparable)
Suggested way forward towards insulin for all (2)

Pharmaceutical industry (originators, biosimilars):

- Guarantee the continued availability of human insulin (continue the production and marketing of human insulin)
- Intra-country differential pricing, with focus on lower prices for public health services and social health insurance
- Ultimate goal: human insulin and analogues at the same public price, allowing for patient choice and meaningful competition
The next problem: diagnostics

Tanzania: one child with DM-1 takes 53% of family income

The cost of insulin is only 25% of the total supply costs (syringes, glucose meter and strips, Hb1Ac testing); glucose test strips (4/day) are 60-65% of the supply costs

Manufacturers (e.g. Roche) supply glucose-meters free of charge to some governments (e.g. Tanzania), diabetes programmes and patients; but the branded glucose strips are unique to the meter and often expensive (US$ 0.25 – 1,00 per strip)
Diagnostic strips in Tanzania

In Tanzania, there are at least three types of glucometers in use: Accucheck (Roche), Trueresult (Nipro) and Contour-Plus (Bayer).

DM-1 patients are advised to use 2-4 strips per day (60-120/month). The National Health Insurance Fund reimburses 25 strips/month. Patients economize on strips, leading to suboptimal glucose control.

Patients may have several glucose meters at home, depending on the strips they can find; but glucose values between meters are inconsistent.
Some uncomfortable questions:

- Why are diagnostic strips so expensive?
- Why is there no competition (glucometers may be free but branded strips are unique and non-interchangeable)?
- Is that a patent / trademark / technical problem?
- Why are there no generic strips? Why no compulsory licenses?
- Is there room for prequalification of generic glucose strips?

- Or should we forget about glucose strips and leap-frog to non-invasive electronic technologies (smart-phone?)
Conclusion, main messages

About half the people who need insulin, cannot get it
The insulin market is extremely concentrated
Insulin analogues are heavily promoted; but clinical benefits do not justify the large price difference with human insulin; very few independent cost / effectiveness studies
The market of biosimilar analogues has great potential, but has not yet led to fair pricing in relation to production costs; biosimilar companies struggle for market share against the big-3
Insulin is a very good test-case for the supply of essential medicines for chronic and non-communicable diseases; the future of insulin supply lies with UHC and social health insurance
Diagnostics (strips) are a very large but even less-known problem
Strong government and UN policies and actions are needed
Acknowledgements and References

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ACCISS toolkit: http://accisstoolkit.haiweb.org