Procela Partners Ltd

Re: RFP 2018.19 - End of Project Evaluation for DNDi Paediatric HIV Grant.

"Market Entry of Improved Paediatric Protease Inhibitor-Based Fixed-Dose Combination for Children with HIV/AIDS"

Grantee: Drugs for Neglected Diseases *initiative* (DND*i*)

Evaluation Report

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12th April 2019.

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NOTE: *the end-of-grant evaluation was completed in Q2 2019 following the closure of all operational activities in December 2018. Content in the evaluation is therefore based on the information that was available at the time the evaluation was done. Since Q2 2019, the 4-in-1 product has been submitted to the US FDA for approval and is currently undergoing a review*.

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Acronyms and Abbreviations

AIS	International AIDS Society
APWG	ARV Procurement Working Group
ART	Antiretroviral Therapy
ARV	Antiretroviral
CHAI	Clinton Health Access Initiative
CLHIV	Children Living with HIV
CRO	Contract Research Organisations
CROI	Conference on Retroviruses and Opportunistic Infections
DAC	Development Assistance Committee
DFID	Department for International Development
DND*i*	Drugs for Neglected Diseases initiative
EGPAF	Elizabeth Glaser Paediatric AIDS Foundation
FDC	Fixed-Dose Combination
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GPRM	Global Price Reporting Mechanism
ICAP	International centre for aids care and treatment programme
ICASA	Independent Communications Authority of South Africa
JCRC	Joint Clinical Research Centre
KEMSA	Kenya Medical Supplies Agency
LMIC	Low- and Middle-Income countries
MPP	Medicines Patent Pool
MSF	Médecins Sans Frontières
NASCOP	National AIDS and STD Control Programme
NCE	Non-Cost Extension
NEPHAK	National Empowerment Network of People Living with HIV/AIDS in Kenya
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
OGAC	Office of the US Global Aids Coordinator
OECD	Organisation for Economic Co-operation and Development's
PADO	Paediatric Antiretroviral Drug Optimization
PDP	Product Development Partnership
PEPFAR	US President's Emergency Plan for AIDS Relief
PHTI	Paediatric HIV Treatment Initiative
PK	Pharmacokinetic
PQ	Prequalification
SAHPRA	South African Health Products Regulatory Authority
SMT	Senior Management Team
TAC	Treatment Action Campaign,
TOR	Terms of Reference
UNICEF	United Nations International Children's Emergency Fund
USAID	United States Agency for International Development
USFDA	United States Foods and Drugs Association
WHO PQ	World Health Organization Prequalification

Executive summary

Context

The purpose of this evaluation is to provide Unitaid with an assessment of the programmatic performance of the Drugs for Neglected Disease *initiative* (DND*i*) *Paediatric* HIV grant including on how successful it has been in bringing to market a child-appropriate ABC/3TC/LPV/r product in granular form approved by a WHO recognised regulatory agency that is available for procurement in Low and Middle Income countries (LMIC). This will also include an assessment of the expected public health benefit and the economic impact, and a review of the outcome of the LIVING and RELIVING studies conducted in Kenya, Tanzania and Uganda.

Historically children and infants have remained an underserved population with access to treatment lagging behind levels achieved for adults. At the time of grant design, the then current data from 2011, estimated that 3.4 million children were living with HIV worldwide, with Sub-Saharan Africa carrying over 90 percent of the global HIV paediatric population. The market for paediatric ARVs was small and fragmented, with the majority of available treatments for the youngest children being sub-optimal. Compared to adult formulations, the much smaller paediatric market was of less interest to manufacturers. In 2013, based on scientific evidence published since 2011, WHO issued formal guidance that LPV/r containing regimens would result in better treatment outcomes, but the only LPV/r formulation available for children unable to swallow tablets was a bitter-tasting syrup, that was toxic due to a high alcohol content and required refrigeration. The net result was low adherence in children switched to LPV/r syrup, and continued reliance on sub-optimal regimens containing the NNRTIs, nevirapine (NVP) and efavirenz (EFV).

In 2013, Unitaid committed up to US$ 17.3 million to the DND*i,* a Product Development Partnership to support the development of an appropriate paediatric HIV drug working with the generic manufacturer Cipla Limited of India (Cipla). The aim was to develop new child-friendly formulations of ABC/3TC/LPV/r[1] and/or AZT/3TC/LPV/r[2] (also known as 4-in-1 formulations) in granules that would lead to the introduction of a new model for administration of medicines to infants and young children. In addition, the project aimed to develop a similar adapted formulation of a standalone pharmacokinetic (PK) booster using ritonavir for children co-infected with TB/HIV.

In the initial phases of the project, and despite very promising preliminary data, the highly anticipated taste-masked 4-in-1 granules developed by Cipla demonstrated low and unpredictable bioavailability, making them unsuitable for further development. In 2015 after two years of development effort, six taste-masked LPV/r formulations with potentially good bioavailability in humans had been identified, and the three most promising formulations were being evaluated in phase l studies in healthy human volunteers.

In 2015 a mid-term evaluation was conducted for Unitaid by the Swiss Tropical and Public health Institute. Following this review, and reprogramming decisions by Unitaid, the Grant, initially programmed for 3 years, was then extended twice, most recently a No Cost Extension (NCE) issued in 2017 and is now in its closeout phase. ***It is this NCE that is the major focus of this evaluation.***

[1] Abacavir, lamivudine and Lopinavir/ritonavir
[2] Zidovudine, lamivudine and Lopinavir/ritonavir

In the light of the challenges experienced in developing taste-masked and bioavailable formulations it was agreed to focus the grant to the development of ABC/3TC/LPV/r only, other planned outputs to develop a stand-alone PK booster (RTV) were also removed from the 2017 NCE. It was no longer considered realistic to complete development of these alternatives in the timely manner to overcome the access barriers targeted by the grant.

In 2015 Cipla Ltd. received USFDA approval of a 2-in-1 LPV/r pellet formulation for use in very young children (0-5 years, or under 25 Kg) that they had developed separately from DND*i*. It was decided to use this 2-in-1 formulation in the LIVING study to be conducted by DND*i* under the Unitaid grant. The purpose of the study being to test the clinical performance of the ABC/3TC/LPV/r regimen in a solid form, and the acceptability of pellets to patients and their care-givers. In 2018, DND*i* also conducted a short qualitative study known as the RELIVING study with caregivers to further explore the acceptability of the pellets among care-givers.

The current position, as at January 2019, is that Cipla has held pre-NDA discussions with USFDA prior to presenting the dossier later in 2019. Cipla is currently preparing a further fasted state study in humans for quarter 2, 2019. Subject to the results of this study, Cipla expect to be able to present the dossier USFDA by September 2019.

On this basis Cipla are hopeful that approval can be granted by late 2019 or quarter 1 of 2020. On this basis Cipla indicate that the product would be launched on the market in quarter 3 of 2020.

Critical Access Barriers

The critical access barriers to be overcome by the grant are defined as:

- **Innovation and availability** – specifically,
    - Has the ABC/3TC/LPV/r child-friendly fixed dose combination in a taste-masked granule form suitable for children unable to swallow tablets been developed?
    - Has the product been tested for safety?
    - Is the product approved by USFDA and/or with WHO Pre-qualification procedure?
    - Is the approved product registered in the majority of high-burden LMICs?
- **Demand and adoption** – drawing on the outcomes of the LIVING and RELIVING studies;
    - Can it be demonstrated that there is a demand in high burden LMICs for the ABC/3TC/LPV/r child-friendly fixed dose combination in a taste-masked granule form?
    - For adoption, can it be demonstrated that patients and their caregivers find the granular product an improvement over the LPV/r syrup?
    - And subject to the product being available will they adopt it?

Additionally, it is recognized that to achieve the necessary scale-up for the envisaged health impact two further issues, not identified in the grant, must be overcome. Namely, Affordability and Supply and Delivery;

- Is production and supply capacity sufficient to meet the demand from LMIC markets?

- Is funding potentially in place to enable procurement of the required quantities at a price acceptable to major funders?

As described above in context to address the key barrier, development of a granular form of the ABC/3TC/LPV/r is at an advanced stage, but it is not yet approved by USFDA or WHO PQ. Therefore, this barrier has not yet been overcome. Consequently, the second availability barrier of registration in high-burden developing countries has also not yet been overcome.

Global funding agencies and procurement agencies in country have confirmed that provided the cost of the 4-in-1 is similar to that of the current 2-in-1 or the LPV/r syrup regimens they will procure the new products when it is available, thus addressing Affordability issue. However, pricing and supply volumes have yet to be negotiated and agreed with Cipla.

The LIVING and RELIVING studies have proved that there is significant potential demand for the child-friendly 4-in-1 in a taste-masked granule form. This is based on the acceptability and the successful clinical outcomes of the separate ABC/3TC and LPV/r 2-in-1 pellets used in the study. It is reasonable to assume that the 4-in-1 granules will be equally acceptable.

Over and above the acceptability within the study, both Kenya and Uganda experienced significant demand for the 2-in-1 pellets from care-givers and implementing programmes. The product is registered for use in both countries and adopted into the national treatment guidelines. Stakeholders in both countries, and others wishing to transition to the pellets, expressed frustration that the available supplies have been insufficient to meet the demand generated by the successful adoption of the product in the studies and communication campaigns.

Tanzania has not yet added the LPV/r pellets to the national treatment guidelines; therefore, demand is more muted than in Kenya and Uganda[3], but the product has been very well received in the study area.

Overall Grant Assessment

Overall the key objective of developing a child-friendly formulation of ABC/3TC/LPV/r as a fixed dose combination in a granular form that can be administered to very young children has yet to be achieved. Development of the desired FDC is at an advanced stage with CIPLA anticipating product launch by mid 2020 subject to US FDA approval.

The degree of difficulty in taste-masking LPV/r and maintaining bioavailability in the granular form was under estimated. Consequently, the original timelines in the grant, and subsequent delivery estimates, all proved to be over optimistic. Numerous optional formulations, incorporating different excipients had to be tried before the current successful formulations was agreed upon. The final formulation used a novel method to produce the taste masked granules. Given how challenging this process was and continued to be, nevertheless Cipla and DND*i* continued to give relatively short timelines in subsequent iterations of the project plan. A more detailed examination of remaining risks, and potential delays, when revising project plans could have tempered what proved to be optimistic targets.

A number of stakeholders advised the evaluators that the succession of missed deadlines had undermined faith in the development process, specifically estimates of when the product would be available for use by patients. This may reduce the commitment to introduce the 4-in-1 when it becomes available, particularly if development of paediatric forms of

[3] The evaluators are also aware that there is significant demand for the 2-in-1 pellets in other countries, but as the activities of the Grant, and specifically the LIVING study only covers Kenya, Tanzania and Uganda, demand from additional countries is not covered in this report.

dolutegravir (DTG)-based regimens appear to be close to completion, registration and launch. However, because DTG use in neonates is not recommended at present, the 4-in-1 may represent an important improvement for the treatment of neonates infected by, or exposed to, HIV.

The evaluators saw little evidence of robust plans at country level for a rapid introduction of and transition to the 4-in-1 granules once approved by USFDA and WHO PQ. At the closure of the grant (December 2018) there was no commitment from Cipla to the level of production planned, or agreement on the price. DND*i* is working with global level stakeholders (e.g. the ARV Procurement Working Group - APWG) to agree a global demand forecast for the 4-in-1 granules. This forecast, and supply availability plans from Cipla will need to be translated into in-country transition plans, but this is not part of the activity of the grant[4].

DND*i* has confirmed to Unitaid and to the evaluators that they are committed to a successful launch of the 4-in-1 granules and will devote their own resources and external funding to ensure this success.

LIVING Study

The LIVING studies conducted at twelve sites across Kenya, Uganda and Tanzania worked well, and enabled generalised conclusions to be reached. Study results from all three countries confirmed that an ABC/3TC and LPV/r 40/10MG pellets regimen produced improved viral suppression in patients regardless of prior treatment exposure and age at initiation. The principal investigators, and their staff found the experience of the study to be rewarding and built in-country capacity. All sites visited or interviewed by the evaluators reported that DND*i*'s management of the studies, their monitoring, mentoring and support were very well received.

To confirm the prima facia acceptability of the pellets to caregivers and CLHIV, DND*i* commissioned a further qualitative study known as the RELIVING study. The study conducted a series of in-depth interviews with groups of caregivers, including mothers, in three sites in Kenya. The RELIVING study reinforced the impressions gained by clinical staff at the study sites that the pellet form of LPV/r was acceptable to the caregivers and the patients, and a significant improvement on the syrup option.

DND*i*'s programme of advocacy and information sharing generated a strong demand for both the 2-in-1 pellets, and potentially for the 4-in-1 granules. The advocacy was well managed and successful in informing countries, implementing agencies and global organisations of the development work on the 4-in-1 granules, and the availability of the 2-in-1 pellets in the interim. The major challenge associated with the study was that due to the coincident timing of the start of the studies, with USFDA approval of the 2-in-1 pellets, and WHO guidance elevating the ABC/3TC/LPV/r regimen to the preferred 1st line treatment led to some confusion in - country. Several countries, including Kenya and Uganda, reacted to the WHO advice, and the expected availability of the pellets, to change their guidelines, and begin a process of transition. However, Cipla had only planned production capacity of up to 30,000 packs per month, far less than the total demand. Additionally, Cipla experienced a series of production difficulties, and have not reliably produced even to that level. The net result of

[4] It became obvious to the evaluators that many stakeholders did not realize that this grant did not cover in-country introduction plans. It is understood that this may be covered by other Unitaid grants, but this position does not appear to be well understood by country stakeholders as yet.

this very difficult supply situation is that countries have had to halt their transition to LPV/r pellets.

Many stakeholders interviewed did not realise that development of the 2-in-1 was not part of the DND*i* grant and associated the LIVING study and DND*i* with the challenges. As a result, DND*i* have felt drawn into the trying to help solve the supply chain challenges, which is something beyond the scope of the grant. The supply situation with the 2-in-1 pellets was particularly difficult to manage in terms of reliable information on production and availability.

Key Findings

- The series of technical challenges encountered with taste-masking a bioavailable 4-in-1 granular formulation mean that the grant has not successfully developed the product to the timetable envisaged in the grant to maximize the health advantages of developing this product.
- On current estimates, obtaining regulatory approval that would enable transition to 4-in-1 to commence in mid-2020 will be approximately 4 years later than envisaged in the original grant signed in 2013
- Development of the product is still relevant for the treatment of paediatric patients, but as a result of the delays, and the advent of DTG-based regimens as the presumptive 1st line treatment, it is now the consensus view among stakeholders that the window in which 4-in-1 will be the preferred 1st line treatment will be limited to around 24 months from launch in mid-2020.
- At this stage the health impact can only be estimated based on a set of assumptions about the speed of transition to the 4-in-1 granules, and the date from which competing treatments based on dolutegravir containing formulations may enter the market. On this basis it is estimated that in the years 2020 and 2021 an additional 19,512, [18,473-20,668] additional children would be in the treatment programs in eight countries analyzed. An increase of about 9% on treatment that can be attributed to switching to 4-in-1. Extrapolating this figure, which represents 48% of the treatment populations to a global level, an additional 41,146 children could be on treatment.
- From the observations of the evaluators and discussions with stakeholders, the LIVING studies appeared to be well conducted, and from the results to date confirm both the acceptability of granules/pellets as a presentation, and the clinical effectiveness of the ABC/3TC/LPV/r regimen in solid form in young children.
- In-country capacity was built in the organisations undertaking the LIVING studies, and, in the individuals concerned, many of whom had not been involved in clinical studies previously.
- Reporting out from the LIVING study has been generally well handled, with a mix of DND*i*'s corporate publications and briefings, and more formal peer-reviewed abstracts and presentations at conferences.

Recommendations

Recommendations to Unitaid

Grant design should leverage the competitive dynamics of the market

It is recommended that, where feasible, future product development grants should support more than one company. This approach will generate competition both in the development process, and support market competition and supply security, once the products are developed and on the market. At the time the grant was designed it was thought that a new paediatric product would not be attractive to multiple generic companies. In practice, for this product, which was envisaged as a new primary 1st line treatment, this did not prove to be the case, with two other companies launching their own development programmes[5]. Options include grants towards the development costs, indicative prices, and working with other agencies to indicate likely demand at launch of the product, e.g. via advance market commitments. This would enable companies to accurately estimate what they could expect to earn from a successful product development.

Grant design should either include robust introduction and implementation plans for the product once developed and approved or be linked to other investments/grants that will support early introduction and implementation plans[6]. This should encompass forecasting of demand, a phased introduction that matches managing demand to available production as it ramps up, implementation tools and guides to national programmes, and other implementers. An active advocacy and advice programme for the post product development period will also be required.

Always select the commercial development partners via a competitive process

The selection of Cipla was made at the recommendation of the grantee based on their existing relations from developing a malaria product, and Cipla's experience in developing other paediatric products. In future all eligible generic manufacturers and other options should be considered in a competitive process to select the company/ies to be supported. The competition could also consider alternative development processes used by innovator, generic companies and others in the pharmaceutical market. As an example, two subject matter experts suggested that Contract Research Organisations (CROs) could be considered as they are more familiar with working to fixed budgets and firm deadlines. It is recognised that CROs only address part of the development process, but it is within that part of the process that some of the major delays in this grant have been experienced.

Compete, or otherwise test, the selection of the grantee to ensure the grantee has the full set of skills and experience necessary to manage the grant

Ensure that the grantee has the full set of skills available, either in-house, via a wider consortium or in cooperation with other stakeholders. This comment reflects statements made by several of the stakeholders interviewed and is included for completeness. It is understood that this is now part of Unitaid's new operating model.

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[5] It was indicated to the evaluators by one company that the existence of the grant support to Cipla was initially discouraging to that company in launching their own development. On further examination they considered the market could be of sufficient size, and as the health need was clear they decided to proceed.

[6] The evaluators are aware that Unitaid has already employed this option in recent grants, but we wanted to reinforce that from the evidence of this grant this approach is a good option.

It was also suggested by stakeholders that Unitaid could take a stronger leadership role in bringing different grantees together when they are operating in the same development and implementation space. The objective being to leverage the best skill sets across different providers. The evaluators appreciate that this is also now part of Unitaid's standard approach.

Maintain flexibility in the grant design and implementation

By definition the full range of challenges in a research and development programme are unknown at the outset. It is therefore essential that the development programme can flex as circumstances change[7]. The programme should include clear development milestones at which progress can be judged, and as necessary the direction of the programme may change, including extending timelines by deliberate decision, not just in reaction to circumstances. More frequent and detailed development milestones may support earlier action to course correct, rather than finding out further down the line that targets have been missed. The design should include the clear option to allow for cessation of the programme, if circumstances are such that it will not be possible to meet the health impact objectives of the grant within time and budget. The contracts between the grantee and the commercial partner responsible for development must include clear targets that reflect the development milestones, with consequences, remedies and as appropriate, penalties for poor performance, and missed milestones.

An increased focus on risk management, scenario planning and risk mitigation in grant design

Although two risks were identified in the Theory of Change, one of which was the major factor in the extensive development delays experienced, DNDi and CIPLA could have more actively managed risks, or robustly explored the impact of different potential delays. It is recommended that grantees be required to prepare a rigorous risk profile based on the well-tried system of assessing Likelihood and Impact of each risk. From this profile the different risks should be plotted against the project plan to identify causal chains, and thus the impact of individual risks to the overall project timetable, and indeed the achievability of the objectives. The risk profile and causal chains should be revisited at 6-monthly intervals, or at major events/challenges in the programme.

Recommendations to grantee

Early agreement on pricing and production capacity is urgent to support a successful introduction of the ABC/3TC/LPV/r granules

To enable countries, funders and implementing agencies to plan their transitions to the new 4-in-1 product it is essential that they know the costs and the timescale against which they can plan.

Prepare a new advocacy and advice programme ready for the launch of the ABC/3TC/LPV/r granules after approval by USFDA

It will be necessary to refresh the advocacy information on the product, the health and clinical advantages, the high level of acceptability of the product by patients and their caregivers, previously issued, and to reassure countries on the supply security of the new product. Countries, and funders need to be confident the supply challenges experienced with the 2-in-1

[7] This is also recognized in Unitaid's new operating model

will not be repeated. This programme of advocacy and advice should include tools and implementation guides for transition for use down to clinic level.[8]

1 Introduction

In November 2018 Unitaid issued a Request for Proposals (RFP) Reference No. 2018.19 to select a suitable contractor to conduct an end of project evaluation for a Unitaid-funded grant to the Drugs for Neglected Disease *initiative* (DND*i*) on "Market Entry of Improved Protease Inhibitor Based Fixed-Dose Combinations for Children with HIV/AIDS" (referred to as the "DND*i* Paediatric HIV grant"). Procela Partners Ltd were successful in their bid to undertake this work and were duly awarded the contract, commencing work on January 7, 2019 with a launch meeting at the Unitaid offices in Geneva, Switzerland, January 14th, 2019.

In accordance with Unitaid instructions to Procela given during the launch meeting, the evaluation, while taking due account of the history of the Grant since award in 2013, focuses on the most recent No Cost Extension (NCE) issued in 2017. This NCE adjusted the required outcomes and reflects Unitaid's then current aspirations for the Grant, and the post-grant impact for the availability of Protease Inhibitor-Based Fixed-Dose Combinations for Children with HIV/AIDS.

The objectives of the evaluation are:

The evaluators will provide Unitaid with an assessment of the programmatic performance of the grant including on how successful it has been in bringing to market a child appropriate approved product by a WHO recognised regulatory agency that is available for procurement in resource limited countries. This will also include an assessment of the expected public health benefit and the economic impact.

1.1 Background to Grant and Overview of Progress

Historically children and infants have remained an underserved population with access to treatment lagging behind levels achieved for adults. At the time of grant design, the then current data from 2011, estimated that 3.4 million children were living with HIV worldwide, with Sub-Saharan Africa carrying the largest burden with over 90 percent of the global HIV paediatric population. The number of newly infected children in 2011 was estimated at 330,000, with 230,000 children suffering AIDS related deaths in the same year. The overwhelming majority of children are infected through mother-to-child transmission.

At the time, the market for paediatric ARVs was small and fragmented, with the majority of available treatments for the youngest children sub-optimal. Major impediments derived from the small market size and consequent lack of manufacturer interest, and with the formulations themselves (bitter, toxic, can require refrigeration, may not be formulated for infants) resulting in low adherence in children.

In Dec. 2012, the Unitaid Executive Board approved the project, and in 2013, the Unitaid Executive Board committed up to US$ 17.3 million to the Drugs for Neglected Tropical Disease *initiative* (DND*i*) to support the development of an appropriate paediatric HIV drug. Unitaid funded DND*i* to develop a new formulation containing a full antiretroviral regimen in

[8]It is recognized that this advocacy and implementation programme may not be undertaken by DND*i*.

an adequate formulation for children who cannot yet swallow tablets; in particular, two FDCs of the WHO-recommended first-line protease inhibitor-based regimen. In addition, the project aimed to develop a similar adapted formulation of a standalone PK booster (ritonavir) for children co-infected with TB/HIV. The aim was to develop new child-friendly formulations in soluble granules that would lead to the introduction of a new model for administration of medicines to infants and young children who cannot swallow tablets. DND*i* contracted Cipla, the India based generic manufacturer, to develop the novel formulations.

The grant incorporated significant level of investment via Cipla Ltd, the commercial partner, in specialised pelleting and other equipment, and purchase of the clinical supplies needed for the LIVING Study. All other product development costs were borne by Cipla Ltd.

In the initial phases the project was challenged by an early failure of the candidate product, and difficulties in finding an alternative compound. In spite of the very promising preliminary data, highly anticipated taste-masked LPV/r granules developed by Cipla demonstrated low and unpredictable bioavailability making them unsuitable for further development. DND*i* worked closely with Cipla Ltd. analysing the failure and testing multiple candidate formulations. After two years of consistent efforts, six taste-masked LPV/r formulations with potentially good bioavailability in humans were identified and the three most promising formulations evaluated in phase l studies in healthy human volunteers.

In 2015 a mid-term evaluation was conducted for Unitaid by Swiss Tropical and Public Health Institute. Following this review, and reprogramming decisions by Unitaid, the Grant, initially programmed for 3 years, was been extended twice, most recently a No Cost Extension issued in 2017, and is now in its closeout phase. ***It is this NCE that will be the major focus of this evaluation.***

In the light of the challenges experienced in developing taste-masked and bioavailable formulations, and as part of this review it was agreed that the original goal to develop two formulations (ABC/3TC/LPVr and AZT ABC/3TC/LPVr) was reduced to focus solely on the ABC/3TC/LPVr 4-in-1 option. Other planned outputs to develop a stand-alone PK booster (RTV) were also removed from the 2017 NCE for the same reason. It was no longer considered realistic to complete development of these alternatives in the timely manner to overcome the access barriers targeted by the grant.

In 2015 Cipla Ltd. received USFDA approval of a 2-in-1 LPV/r pellets for use in very young children. This has been introduced to the market and was used in the LIVING and RE-LIVING studies conducted by DND*i* under the Unitaid grant. The 2-in-1 product was not part of the product development goals of the DND*i* Paediatric Grant, but has been used in combination with paediatric ABC/3TC within the LIVING study to evaluate the effectiveness of pellets as an alternative to LPV/r syrup in children below 3 years and/or 25KG, who cannot swallow tablets.

The much anticipated 4-in-1 formulation, the main target of the Unitaid grant, is now at an advanced state of development.Provided a positive outcome of the registration file, approval is anticipated by late 2019 or quarter 1 of 2020. On this basis Cipla indicate that the product would be launched on the market in quarter 3 of 2020.

1.2 Grant Objectives and Outputs

The original objectives of the Unitaid DND*i* Paediatric HIV grant were:

Goal/Impact: To make available optimal first line ART for young infants and children (defined as children who cannot swallow pills and are under the 25kg weight band).

Primarily Outcome: Optimally formulated 4-in-1 available in endemic countries

Output 1: Formulate an optimal PI-based ARV FDC (ABC/3TC/LPV/r)
Output 2: Clinical studies initiated for 4-in-1 ARV/FDC (ABC/3TC/LPV/r)
Output 3: Registration of adapted paediatric ABC/3TC/LPV/r for use in resource poor settings;
Output 4 Formulate a standalone PK Booster (RTV)
Output 5: Clinical studies completed for a stand-alone PK booster (RTV)
Output 6: Registration of an adapted paediatric RTV granules for use in resource-poor settings
Output 7: Facilitate the adoption of LPV/r based first-line ART and better adapted RTV formulation for super-boosting HIV/TB co-infected children in countries

Under the terms of the 2017 NCE, outputs 4, 5 and 6 were removed from the project plan in 2016, during the first no-cost- extension; there was no budgetary implementation under these outputs. ***This evaluation, therefore, only reports on Outputs 1, 2, 3 and 7.***

Evaluation Findings

2.1 Results against Grant Outputs

This evaluation is focused on the objectives and outputs agreed in the No Cost Extension of the grant issued in 2017. However, for completeness, the results tables incorporate Outputs and Activities from the original grant and the No cost Extensions. The commentary and recommendations will be primarily drawn from the activities and outcomes achieved during the period of the 2017 No Cost Extension.

2.1.1. Output 1: Formulate optimal PI-based 4-in-1 FDCs (ABC/3TC/LPV/r)	
Activity	Results as at end of project
Activity 1 - Weight Band Dosing	***Completed***, recommended weight band dosing was proposed and accepted in 2013
Activity 2: Development of LPV/r granules plus NRTI granules into 4-in-1 **2.1** Preclinical toxicology study to support currently available safety data on one excipient used in the LPV/r formulation **2.2** Stability study	Development of the selected formulation of 4-in-1 granules was completed in 2017 after experimentation with several options to ensure effective taste-masking and use of different ratios of API/EPO polymer. 2.1 ***Completed*** 2.2 ***Completed***
Activity 3: Clinical batches produced for 4-in-1	***Completed*** 2017 and 2018

Activity 4: Registration stability studies for 4-in-1 (accelerated and real-time)	During 2018, after the manufacture of the regulatory batches, the Chemical, Manufacturing and Controls file[9] of the 4-in-1 dossier was compiled and the first stability data table generated (3 months' and 6 months' data will be available at the end of January 2019).

2.1.2. Output 2: Complete clinical studies on 4-in-1 FDCs (ABC/3TC/LPV/r)	
Activity	Results as at end of project
Activity 1: Pilot bioavailability studies conducted with 4-in-1 ARV FDC in Healthy Human Volunteers	Conducted in the PATHFINDER study- **Clinical Study** Initiated: 19 September 2017 ***Completed:*** 28 September 2017 **Bioavailability Study** Experimental start date: 13 October 2017 for LPV/r Experimental start date: 17 October 2017 for ABC/3TC ***Completed***: 31 October 2017 for LPV/r ***Completed*** date: 27 October 2017 for ABC/3TC
Activity 2: Pivotal bioequivalence/ bioavailability study conducted with 4-in-1 ARV FDC in healthy human volunteers **2.1:** *Fed state study using pilot GMP batch (India)* ***2.2:*** *Fed and Fasted state pivotal studies using registration/ industrial batches (India)*	The three pivotal registration batches were made in May 2018 and submitted to thorough analytical control to assure that the analytical assay values were in line with the FDA recommendations for a bioequivalence trial. Both pivotal studies were performed in July 2018 on 36 adult volunteers for the study in fed conditions (Activity 2.1) and 60 adult volunteers in fasted conditions (Activity 2.2). The results of the pivotal studies were reviewed with USFDA in pre-NDA discussions at the end of December 2018. A further study is planned for Q2 2019. Subject to the results of these studies Cipla anticipate that they will be able to provide dossiers to USFDA by September 2019. Assuming acceptable results approval is hoped for by end 2019, or Q1 2020.
Activity 3: Phase l/ll PK study in children to confirm adequate exposure to all components of the 4-in-1 [conducted in Uganda & South Africa]	Known as the LOLIPOP 1 Study, which will now only be performed in Uganda, not South Africa as planned. Unitaid granted DNDi a funding extension for this study until the end of March 2019. Approval from the National Drug Authority in Uganda took longer than anticipated, but was received in January 2019. As a result, this study cannot now be started before the end of March 2019 and will fall outside of the grant period. DNDi will fund the

[9] CMC, *(part of new pharmaceutical product application to the US Food andDrug Administration)*

	completion of this study through its own means or through other external funding.

2.1.3 Output 3: Registration of an adapted paediatric ABC/3TC/LPV/r FDC for use in resource-poor settings	
Activity	Results as at end of project
Activity 1: Regulatory scientific advice	DND*i* has worked closely with Cipla to support preparation of necessary documentation for approval by USFDA.
Activity 2: Preparation and submission of regulatory dossiers for 4-in-1 FDC	***Outstanding***. This activity cannot be commenced until the product dossiers are approved by USFDA and WHO Pre-qualification. Key countries are aware of the development from DND*i* and other advocacy and information sharing activities. The advent and successful adoption of the 2-in-1 pellets in the LIVING STUDY, and in selected government programmes, and the competing 2-in-1 granules by some government and NGO programmes has also shown the potential for this type of presentation.

2.1.4 **Output 4: Formulate a standalone PK Booster (RTV)** – This output was dropped from the grant objectives in 2016 due to series of failures of bioavailability in tests using rats. DNDi abandoned plans for further development of a standalone RTV booster. Taking into consideration newly developed and approved formulations of RTV suitable for young children, further development of the taste-masked RTV granules, while it could be beneficial, was considered by the international community and other partners to no longer be a priority for paediatric ARV drug development. As a result, it was removed from the grant as an output under the 2016 and 2017 NCEs.

2.1.5 **Output 5: Clinical studies completed for a stand-alone PK booster (RTV)** – This output was dependent on completion of Output 4, which was deleted from the grant.

2.1.6 **Output 6: Registration of an adapted paediatric RTV granules for use in resource-poor settings** - This output was dependent on completion of Outputs 4 and 5, which were deleted from the grant.

2.1.7 Output 7: Facilitate the adoption of LPV/r-based first-line ART and better adapted RTV formulation for super-boosting HIV/TB co-infected children in countries	
Activity	Results as at end of project
Activity 1: RE-LIVING 1 − Realistic evaluation of acceptability and adherence to paediatric antiretroviral treatment in the form of pellets (LPV/r)[Kenya]	Study conducted in 2017/18. Results have been collated and are awaiting publication. Informal indications from DND*i* are that the results of the study will be positive. However, reports from other countries indicate that care givers prefer granules to the pellet formulation, but both are far preferable to the LPV/r syrup.
Activity 2: Implementation studies - Prospective study of Lopinavir-based ART for HIV Infected children globally (LIVING study)	For practical reasons the LIVING study was conducted in three countries only using the Cipla produced LPV/r 40/10mg pellets (the 2-in-1 option). ***The studies in those countries were successful*** with results proving the acceptability, safety (no SAEs due to the pellets) and effectiveness (adherence and viral load results showed improvements in all children, regardless of prior treatment exposure
a) Kenya	Study activities ***completed*** in December 2018
b) Tanzania	Study activities nearing a close, expected inn quarter 2 2019.
c) Uganda	Study activities ***completed*** in December 2018
d) South Africa	***Not conducted***
e) Super-boosting 2 study S. Africa	***Not conducted***
f) Testing Mylan product	***Not conducted***
Activity 3: Clinical study in children for registration of 4-in-1 in India	***Not conducted.*** Cipla made the decision to await the receipt of USFDA approval to see if this study is required, or whether the USFDA approval will be sufficient to support registration of the 4-in-1 in India
Activity 4: Undertake 4-in-1 access activities	To prepare country programmes and implementation partners for availability of the 4-in-1, DND*i* has carried out a comprehensive awareness, advocacy and information sharing programme regarding the need for optimal paediatric formulations, with

Activity 4: Undertake 4-in-1 access activities continued…	particular focus on the expected benefits from the proposed 4-in-1 formulation. This has consisted of attendance at, and contributions to global level meetings mostly in Geneva, including Paediatric Antiretroviral Drug Optimization (PADO), Paediatric HIV Treatment Initiative (PHTI) and the ARV Procurement Working Group (APWG). *DNDi* has also presented papers and abstracts at internal conferences, including the International AIDS Society bi-annual meeting in Durban (2016) and Amsterdam (2018), CROI annual meetings, and at ICASA (2017). They have also published in peer reviewed journals and via their own website and other means. See annex 8 for a list of publications supplied by DND*i*. More direct actions to support adoption are not appropriate until the approval is obtained from USFDA and the product is pre-qualified by WHO, at which point direct support to countries to define their needs, register the product in country and coordinate supply with other major buyers and funding agencies becomes appropriate.

2.2 Access Barriers

The key access barriers to be overcome by the grant are defined as:

- **Innovation and availability** – specifically,
    - Has the ABC/3TC/LPV/r child-friendly fixed dose combination in a taste-masked granule form suitable for children unable to swallow tablets been developed?
    - Has the product been tested for safety?
    - Is the product registered with USFDA, and the WHO Pre-qualification?
    - Is the approved product registered in the majority of high-burden LMICs?
- **Demand and adoption** – drawing on the outcomes of the LIVING and RELIVING studies;
    - Can it be demonstrated that there is a demand in high burden LMICs for the ABC/3TC/LPV/r child-friendly fixed dose combination in a taste-masked granule form?
    - For adoption, can it be demonstrated that patients and their caregivers find the granular product an improvement over the LPV/r syrup?
    - And subject to the product being available will they adopt it for use?

The following table assesses the outcomes from activities under the grant to address the **Innovation and Availability** barriers and the strength of evidence for the results. The strength of evidence shown is based on the degree of consensus from the evidence gathered and the opinions expressed in interviews, and the number of stakeholders expressing the view. Where the interviewee is considered by their peers and by the evaluators to be a subject

matter expert, greater weight was given to their comments. For example, comments from normative agencies, and major funders, or from entities engaged in international groups in areas such as forecasting, and product adoptions were considered subject matter experts.

Context	The treatment of children living with HIV lags behind the results achieved for adults. Part of the challenge is that for very young children, birth to 3 years or under 25KG, there is no FDC of the preferred 1st line therapy ABC/3TC/LPV/r (4-in-1) in a child friendly presentation. LPV/r is a particular challenge as the only available formulation is a bitter tasting syrup that requires refrigeration and has high alcohol content. The DND*i* grant was designed to make available ABC/3TC/LPV/r in a child friendly formulation working with Cipla Limited of India as the commercial development partner.
Activities	• Cipla Ltd developed a 4-in-1 candidate suitable for children in the target age group • Cipla has conducted a number of clinical studies to test various formulations of the proposed product. Challenges with early formulations led to significant delay in overcoming the innovation barrier • DND*i* supported Cipla in addressing the technical challenges in developing the 4-in-1 formulation, specifically in taste-masking, bioavailability and bioequivalence • Cipla Ltd has submitted held pre-NDA discussions with USFDA. The current status is that another fasted stated bioavailability study is being prepared by Cipla, the results of this study are targeted for submission to USFDA in September 2019 • DND*i* has kept countries and other stakeholders aware of development progress, but until the product is approved by an SRA and/or WHO PQ in-country registration cannot commence
Contribution	• Cipla's contribution to development of the 4-in-1 product has been extensive over the period of the grant, but their management and responsive to subsequent delays could have been more effective • It is difficult to judge the extent of DND*i*'s contribution to overcoming the technical challenges in developing a successful 4-in-1 formulation, but it is concerning that the various delays have caused the project to overrun by over 3 years reducing the window available for the product to make a public health impact before the expected introduction DTG-based formulations for young patients.

	• Cipla has submitted the required documentation to USFDA and held meetings to discuss the most appropriate approach that would enable a priority review of the application. • DND*i*'s contribution to support widespread registration of the new product in LMICs countries has as yet been limited to information sharing and advocacy. Direct engagement to support in-country registration can only commence once approval is granted by USFDA and WHO PQ.	
Evaluation of overall progress	**Cipla has not yet been effective in developing a child-friendly granular formulation of 4-in-1 product within the timeframe of the grant.** As described earlier in this report, a series of technical challenges were encountered in successfully masking the bitter taste of LPV/r, while maintaining the required bio availability. It is acknowledged that all research and development of new drugs is difficult, and the extent of challenges can never be known with confidence at the outset, but the extensive delays in this project have adversely impacted the likely health impact from introduction of the formulation.	***SoE*[10]** 
	Slow progress is being made in achieving registration of the new 4-in-1 product with the USFDA, although the latest delay delay to at least September 2019 is a disappointing setback. The strategy of first pursuing USFDA approval and then applying to WHO PQ on the basis of the USFDA approval is sound, and one pursued by other generic companies.	
	The LIVING study data indicate that rates of viral suppression in patients on the ABC/3TC/LPV/r with LPV/r pellet form are stronger than for patients on LPV/r syrup. The same holds true for patients previously on NVP containing regimens for whom the clinical outcomes are radically better. It is expected that these results will be replicated with the 4-in-1 in granular form.	
	No progress has been made in the registration of the 4-in-1 product in countries, which cannot be commenced until USFDA and WHO PQ approval is obtained	
	It is not yet clear what level of production capacity Cipla will make available for the product at launch. As a result it is not possible to say if production capacity will be a barrier.	
	Pricing for the new product has yet to be agreed. As a result it is not possible to say if the price of the product will be a barrier.	

The requirement by USFDA for a further fasted state study will likely delay approval until at least the end of 2019, and possibly into quarter 1 of 2020. On this basis it is assumed that the earliest the 4-in-1 will be available in commercial quantities is quarter 3 of 2020.

[10] Strength of Evidence

The following table assesses the outcomes from activities under the grant to address the Demand and Adoption barriers and the strength of evidence for the results.

Context	As a new product it is important to understand: • The level of demand at launch, • How this may grow, • If the product is acceptable to the patients, their caregivers, and to the supporting health system. As a surrogate for 4-in-1 granules DND*i* conducted two studies to assess the demand and adoption using ABC/3TC and another product developed independently by Cipla, the LPV/r (2-in-1) in pellet form.
Activities	• DND*i* organized and managed the LIVING study in three countries to assess the acceptability and effectiveness of the four-drug combination of ABC/3TC/LPV/r, albeit not in a single fixed dose. Studies were run at twelve sites across Kenya, Uganda and Tanzania. • Data has been collated centrally in Kenya by DND*i*, and will be reported out later in 2019 • Interim results have been presented by DND*i* at international conferences and local events by some of the Principal Investigators from the study sites. • DND*i* launched the RELIVING study in 2018, at three sites in Kenya, to assess the acceptability of the pellet presentation to caregivers and children. This was a qualitative study conducted by interview by social scientists. The results have been presented in two poster session at the IAS Conference in Amsterdam, reporting positive results, and high levels of acceptability with patients and their caregivers[11].
Contribution	• DND*i*'s contribution in managing the LIVING study has been strong, although some delays were experienced in achieving approval from the national governments to establish the studies, and in the recruitment of eligible children to the study. • The LIVING study has made a strong contribution in demonstrating the effectiveness and acceptability of the pellet presentation as a

[11] : https://www.dndi.org/2017/media-centre/scientific-articles/scientific-articles-paediatric-hiv/bmj_acceptabilityandadherence_phiv_new_pellet_formulation/

	replacement for the current standards of care, including LPV/r syrup. There is a strong demand in Kenya and Uganda for the pellets in the national programme. Less so in Tanzania, as the national government has not yet adopted the pellet presentation of LPV/r into their national guidelines. • The RELIVING study has confirmed strong acceptability of the pellets with both patients and their caregivers.	
	Demand - The LIVING study had a strong impact demonstrating the acceptability of the pellet product by patients, caregivers and the health systems. As a result there is a strong demand in Kenya and Uganda for the 2-in-1 product,	***SoE*** 
Evaluation of overall progress	which is expected to translate into a strong demand for the 4-in-1. It is not yet possible to say if this will be the case in Tanzania, but acceptability and demand is high in the area of the study site. The RELIVING study report is expected to reinforce these results	
	Adoption - The LIVING study results and the fact that Kenya and Uganda, and many other countries, have already adopted ABC/3TC/LPV/r into their national guidelines indicate that the 4-in-1 when available will be adopted. The lack of adoption in Tanzania is not considered to be an issue of policy or resistance to adopt, but simply a matter of time to process.	***SoE*** 

The results from the LIVING study are strong, but there have been adverse effects into the national programmes in Kenya and Uganda due to severe supply constraints for the 2-in-1 product from Cipla. The national programmes have been unable to switch patients to the 2-in-1 products as they would have wished from the success of the LIVING study, and the patient and caregiver demand generated around the study sites and elsewhere in the two countries.

In 2013, before the LIVING studies commenced, WHO issued guidance strengthening their advice that countries should transition paediatric patients to LPV/r containing regimens, and at almost the same time the Cipla developed 2-in-1 was granted tentative approval by USFDA. With the advent of the LIVING study it rapidly became apparent that the pellets presentation of LPV/r was significantly preferable to the syrup, and this had the effect of releasing the latent demand in the community for patients to switch to the pellets. This is, of course, very encouraging, but Cipla experienced some continuing production difficulties, such that they have been unable to meet the demand, and according to reports to the evaluators by procurement entities have consistently failed to meet their delivery promises. As a result, transitions to LPV/r pellets had to be stopped outside of the LIVING study, and procurers and national programmes say they have lost faith in the company to meet its commitments.

The use of the 2-in-1 product in the LIVING study has also caused some confusion in the stakeholder community as to the scope of the DND*i* grant. Many of the organisations interviewed did not appreciate that the grant did not cover development of the 2-in-1 product. This caused confusion as to accountability for the supply delays, and who should take responsibility.

In light of this experience it will be essential to ensure that demand forecasts for the 4-in-1 are robust, and that Cipla's production capacity is clearly established, and for the company to be held to account to meet the delivery requirements. From interviews, the evaluators anticipate that donors, procurers and national programmes will be very cautious in their approach to transition to the 4-in-1 until Cipla establishes a strong record of supply security for the product.

From outside the DND*i* grant several interviewees who are aware of the situation in other countries have advised that a competing 2-in-1 product from Mylan in granular form was often preferred to the pellets, especially for young recently weaned patients who could feel a "grittiness" from the pellets, which are larger than the granules. As yet this is anecdotal information, rather than from comparative studies, but it is possible that demand for the pellets may be lower than anticipated from the success of the LIVING study. However, these reports of preference for granules over pellets does further indicate that the ABC/3TC/LPV/r regimen in granular form will be highly acceptable and readily adopted by countries.

Additionally, it is recognized that to achieve the scale up necessary to gain the health impact envisaged by the grant two further issues, not identified in the grant, must be overcome. Namely, Affordability and Supply and Delivery

- Is production and supply capacity sufficient to meet the demand from LMIC markets?
- Is funding in place to enable procurement of the required quantities at a price acceptable to the major funders?

It is essential that the issues of production capacity and price are resolved soon to enable countries, donors and major procurement agencies to plan a phased transition process to introduce the 4-in1.

With regard to price, the major donors have indicated that one of the assumptions is that the pricing target is no higher than the current price for Kaletra syrup, and that this will be acceptable.

Both major donors, PEPFAR and The Global Fund for AIDS, TB and Malaria, align with WHO treatment and clinical normative guidance in their procurement policies, thus they expect to procure the 4-in-1 when it is available. However, there will be no overall increase in PEPFAR country budgets, or Global Fund grants specifically to accommodate any increase in unit prices, or the cost per patient per year from switching to the 4-in-1. Countries will therefore have to adapt their budgets accordingly. Compensating factors are that due to the improved efficacy of the ABC/3TC/LPV/r regimen the impacts of treatment failure and toxicity will be lower. It is also expected that logistics costs, and wastage will be lower due to the improved handling of the granules compared to LPV/r syrup. These systems savings were not part of the grant objectives, or this evaluation. The majority of stakeholders anticipate that over time the volume of new very young patients will decline due to the beneficial effects of PMTCT programmes when a significantly increased number of babies born to HIV+ mother will be born HIV negative. All of the LIVING studies reported difficulties in recruiting HIV+ babies under 6 months due to this factor.

2.3 Public Health and Economic Impact Assessment

The purpose of this analysis is to estimate the anticipated level and the public health impact of the uptake of 4-in-1 pellets in the treatment of paediatric HIV infection. It is currently expected that 4-in-1 will be introduced in the market from 2020. Its subsequent scale up and impact under different scenarios, until the expected introduction of DTG-based regimens from 2022 is also estimated, with the caveat that the actual impact could be less as not all countries will be able to switch to 4-in-1 immediately.

A more accurate estimation will only be possible when the rate of production and launch price are agreed by the manufacturer, and it is known when and at what pace countries plan to transition. The pace will depend on in-country plans, and availability of the product. As noted elsewhere in the report, procurement funding is not expected to be a barrier.

Three scenarios were simulated on the patient population of eight countries, Botswana, Kenya, Nigeria, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe which, based on UNICEF[12] data, were home to 48.7% of all incidence of paediatric HIV infections globally in 2017. These countries were chosen to achieve a representative mix based on burden of disease, development/income level, and level of coverage for mother to child transmission programs.

Scenarios are:

1) Fast Track adoption, transition is very fast
   - Starting in 2020, 100% of all children initiating ART are started on 4-in-1
   - Starting in 2020, 80% of children already on ART switch to 4-in-1 in the first year.
   - *In 2022, 20% of all children initiating ART and 20% of all children already on ART are switched to DTG based regimen.*

2) Intermediary course
   - Starting in 2020, 40% of all children initiating ART are started on 4-in-1
   - Starting in 2020, 40% of children already on ART switch from standard care of treatment to 4-in-1. In subsequent years the same number of children already on ART is switched to 4-in-1, until 4-in-1 reaches a market share of 80%. This takes two years.
   - *In 2022, 40% of all children initiating ART and 40% of all children already on ART are switched to DTG based regimen.*

3) Conservative scenario (due to slow adoptions and supply side problems)
   - Starting in 2020, 20% of all children initiating ART will start 4-in-1
   - Starting in 2020, 20% of children already on ART switch from standard of care treatment to 4-in-1 in year one. In subsequent years the same number of children is switched to 4-in-1.
   - *In 2022, 80% of all children initiating ART and 80% of all children already on ART are switched to a DTG based regimen.*

In the first part, the incremental number of children that would be retained on treatment due to better adherence, acceptability, and fewer lost to follow-up of the 4-in-1, compared to current standard of care treatment is calculated.

The retention rate of 90% is based on results from the LIVING study. The retention rate includes, acceptability, adherence, and mortality rates[13].

[12] For every child, HIV Epidemiology among children and adolescents, 2017; at: data.unicef.org
[13] DND*i* LIVING study data

In the second part of the analysis we calculate the incremental cost-effectiveness of 4-in-1 as opposed to standard of care treatment in the countries under consideration. The output is the incremental cost-effectiveness ratio (ICER) per life year gained, by switching to 4-in-1.

Part I: Incremental number of children in the treatment programs and number of life years gained by switching to 4-in1.

The following data were considered in the impact assessment:

Number of new infections in the eight countries for 2015, 2016, and 2017

Number of new cases of HIV infections in children between the ages of 0-14 for 2015, 2016 and 2017 in the eight countries, were obtained from UNICEF[12]

Retention rates for the standard of care treatments and that of 4-in-1

Retention rate on ART, was taken to be 75% annually, for children not using LPV/r pellets, as evidenced by a study in Zimbabwe for under 4-year olds[14]. For children using LPV/r pellets, 90% annually from the LIVING study was applied[15].

The retention rate of 75% from a study in Zimbabwe was used because the age range of children included was close to that of the LIVING study. This rate is in the range of retention rates reported in a systematic review, by Abuogi et al, which looked at twelve studies in an African setting, with a total of 31,877 children under the age of ten. They found that retention rates for one year ranged between 71-95%[16]

In the sensitivity analysis we assessed what effects increasing or decreasing the number of children starting treatment each year by 5% would have on the outcome.

Please see annex 5 for more details on the methodology.

Table 1: Assumptions

Assumptions	**Source of information on which assumptions are based.**
Price of 4-in-1 will not be more than the current price of LPV/r 2-in-1 pellets per treatment year, (unit price of $19.20 or $467.20 per treatment year)	DNDi and Pooled Procurement Mechanism Reference Pricing: ARV[17]
All new infections in children (0-14) reported are in under five-year olds	UNICEF27
We assume that in 2022, the switch from 4-in-1 to a DTG-based regimen will not generate additional benefits in terms of adherence, acceptability, thus retention. The retention rate will be similar for both products (~90%)	DTG assumption by evaluator due to absence of data
At any one point in time the market share of 4-in-1 is capped at a maximum of 80% - the remaining market share in this age group being for other products.	Based on APWG forecast

[14] http://www.unaids.org/sites/default/files/country/documents/ZWE_narrative_report_2016.pdf
[15] LIVING study - data provided by DNDi
[16] Abuogi LL, Smith C, McFarland EJ (2016) Retention of HIV-Infected Children in the First 12 Months of Anti-Retroviral Therapy and Predictors of Attrition in Resource Limited Settings: A Systematic Review. PLoS ONE 11(6): e0156506. doi: 10.1371/ journal. pone.0156506
[17] https://www.theglobalfund.org/media/5813/ppm_arvreferencepricing_table_en.pdf

We included children from age 0-5 to switch to 4-in-1 if the switching scenario required them to do so – above age 5, children were not included in the impact and cost-effectiveness assessments	DNDi LIVING study shows a ¼ of children recruited were more than 5 years, and based the recruitment not on age, but weight (3< and> 25kg) and inability to shallow.
We assume that production capacity for 4-in-1 will be sufficient to satisfy demand.	Evaluators
It is assumed that the number of life years gained by switching from EFV based regimen is similar to that of switching from a NPV based regimen.	Evaluators, due to lack of data

Results

In the eight countries modelled, the benefits of switching to 4-in-1 were mainly in increased survival on treatment. This is illustrated in table 2 below. Calculations go up to 2021 because of the expected introduction of GTD-based regimen in 2022.

Table 2: Incremental number of children on treatment gained by switching to 4-in-1 from standard of care treatment in 2020 and 2021 in the eight countries

Scenarios	Rate of adoption	Total number of children on treatment 2020&2021	Number of children on 4-in-1 2020&2021	*Incremental number of children on treatment gained by switching to 4-in-1, in 2020 & 2021
Fast track scenario	In 2020, 100% of all children initiating ART and 80% of children already on treatment switch to 4-in-1.	**216,867**	**187,337**	**28,101** [**26,283-30,051**]
Intermediary course scenario	In 2020, 40% of all children initiating ART and 40% of children already on treatment switch to 4 in 1.	**216,867**	**129,997**	**19,500** [**18,210-20,886**]
Conservative scenario	In 2020, 20% of all children starting treatment, 20% of existing children on treatment switch to 4 in 1.	**216,867**	**64,998**	**9,750** **[8,584-10,443]**

*Lowest and highest estimates reflect a 5% decrease and increase respectively of children initiating ARVs each year, from the sensitivity analysis.

For the fast track scenario, the gains from switching is seen to be 28,101 children or 14,051 children annually.

For the intermediary course scenario, the number of additional children on treatment is 19,500 over a period of two years, or 9,750 children annually.

For the conservative scenario 9,750 more children are on treatment due to switching to 4-in-1 over two years or 4,875 children annually in the eight countries.

There is a 13% increase in number of children in treatment programs that can potentially be attributed to switching to 4-in-1 in the fast track scenario, 9% in the intermediary course scenario and 5% in the conservative scenario.

Using the composition of treatment in the eight countries, please see table 4 (Cost of different treatment regimens), and the number of life years gained by switching from standard of care treatment calculated, please see table 5 (Incremental cost/life year of switching to 4-in-1 in the 8 countries), we calculated the total number of life years gained in 2020 and 2021 in the three scenarios; please see results in table 6, in annex 5, section 5.3.

For the two years 2020 and 2021, before the expected introduction of the DTG based regimen, 28,603 life years are gained in the eight countries in the fast track adoption, 19,848 in the intermediary course scenario adoption, and 9,924 life years in the conservative scenario.

This analysis covered 48.7% of all incident paediatric HIV infections globally for 2017; taking the intermediary scenario as the most likely and extrapolating the impact globally would potentially result in 40,756 more children on treatment in the two years, 2020 and 2021 that could be attributed to switching from standard care of treatment to 4-in-1, bearing in mind that settings will be different from the countries in our analysis, and that new incidence trend could change.

Whether the above scale up scenarios, numbers treated with 4-in-1 and impacts prove to be realistic depends inter alia on therapeutic competition; it is expected that in 2022 a new paediatric formulation of DTG fixed dose combination will become available with similar effectiveness, equal user-friendliness and possibly even a reduced cost.

Thus, in the following section we look at the potential effects of introducing a DTG-based regimen on the scale-up of 4-in-1.

Impact and numbers treated in 2022, 2023 and 2024

Table 3 shows results of the impact the introduction of DTG based regimen will potentially have on the market size of 4-in-1.

As the retention on treatment with DTG based regimen is assumed to be the same as that of 4-in-1, the introduction of DTG would not increase survival or retention but would result in a decreased uptake of 4-in-1. Considering the results of overlaying DTG introduction scenarios on the fast track scenario, described above, the uptake of 4-in-1 will be reduced by 40% to 42,250 children by 2024, (from 93,421 in 2021).

In the intermediary course scenario, the uptake of 4-in-1 would be reduced from 86,499 in 2021 to 21,125 remaining in 2024, equivalent to 20% of the market share.

In the conservative scenario, the uptake of 4-in-1 would also be reduced to 21,125 from 43,250, keeping a market share of 20% by 2024.

This assessment is comparable with assessments by the APWG in their forecast for the uptake of 2-in-1 pellets, if one takes into account that market size assessment considers children < 5 years of age as the target group for the 4-in-1, whereas the APWG considered children < 3 years of age as its target group. Our assessment should therefore be expected to come out about 40% higher. The larger target group for 4-in-1 is used to be consistent with the LIVING

study, which included children on the basis of their inability to swallow tablets, enrolled children with mean age of 3.3 years, of which 25% were older than 4.8 years of age at enrolment.

Table 3: Effects of introduction of DTG based regimen on scale-up of 4-in-1								
Fast- (optimistic scenario)- For description of fast track please refer to text above	**2020**	**Baseline year-2021 - number of Children on treatment**	**Expected introduction of DTG based regimens-2022**	***Market share of 4-in-1 in 2022**	**2023**	***Market share of 4-in-1 in 2023**	**2024**	***Market share of 4-in-1 in 2024**
Number of children on 4-in-1	93,916	93,421	84,499	80%	63,375	60%	42,250	40%
Number of children on DTG based regimen	00	00	21,125	20%	42,250	40%	63,375	60%
Number of children on Other regimens (LPV/r liquid formulation, LZ)	14,827	14,703	-	-	-	-	-	-
Total number of children on treatment	108,743	108,124	105,624	100%	105,624	100%	105,624	100%
Intermediary (Central scenario)- For description of intermediary track please refer to text above	**2020**	**Baseline year-2021 - number of Children on treatment**	**Expected introduction of DTG bade regimens-2022**	***Market share of 4-in-1 in 2022**	**2023**	***Market share of 4-in-1 in 2023**	**2024**	***Market share of 4-in-1 in 2024**
Number of children on 4-in-1	43,497	86,499	63,375	60%	21,125	20%	21,125	20%
Number of children on DTG based regimen	00	00	42,250	40%	84,499	80%	84,499	80%
Number of children on Other regimens (/ LPV/r liquid formulation, NLZ)	65,246	21,625	-	-	-		-	-
Total number of children on treatment	108,743	108,124	105,624	100%	105,624	100%	105,624	100%
Conservative (Pessimistic scenario)- For description of conservative track please refer to text above	**2020**	**Baseline year-2021 - number of Children on treatment**	**Expected introduction of DTG bade regimens-2022**	***Market share of 4-in-1 in 2022**	**2023**	***Market share of 4-in-1 in 2023**	**2024**	***Market share of 4-in-1 in 2024**
Number of children on 4-in-1	21,749	43,250	21,125	20%	21,125	20%	21,125	20%
Number of children on DTG based regimen	00	00	84,499	80%	84,499	80%	84,499	80%
Number of children on another regimens (/ LPV/r liquid formulation/NLZ)	86,944	64,874	-	-	-	-	-	-
Total number of children on treatment	108,743	108,124	105,624	100%	105,624	100%	105,624	100%

*Market share of number of children on treatment

Part II: Incremental Cost effectiveness ratio, ICER associated with switching to 4-in1.

In part II we calculated the incremental cost-effectiveness of switching to 4-in-1 as opposed to standard of care treatments in the eight countries. The output is the incremental cost-effectiveness ratio (ICER) per life year gained.

The regimens used in the eight countries were inferred from their procurement behaviour in 2017 as reported in Global Price Reporting Mechanism, GPRM.[18]

Using guidelines from the weight-based dosing for ARV formulations for infants and children from WHO guidelines[19] , the cost of the NRTI component of different regimens is calculated as the cost of ABC+ 3TC 60/30 mg, ZDV+3TC 60/30 mg, ZDV 60 mg, ABC 60 mg, the latter 3 complemented with 3TC 10 mg/ml, weighed for the volume of the ABC and ZDV components) for a 12.7 kg infant, based on the GPRM data of 2017. We used the weight of 12.7 kg because it was the median weight of children in the LIVING study. To this we added the cost of other formulations needed to make a full regimen, and thus its treatment cost per year. Please see table 4 below:

Table 4: Cost of different treatment regimens

Regimen	Annual cost NRTI component(USD)	Annual cost NVP, EFV, or LPV/r(USD)	Cost per patient, per treatment year(USD)	Percentage using regimen according to GPRM data 2017
AZT+3TC+NVP (3 in 1) regimen	Not Applicable	Not Applicable	72	17.6
NRTI+ NVP 50mg regimen	100	61	161	5.0
NRTI+ NVP 10mg/ml regimen	100	96	196	5.5
NRTI+ EFV regimen	100	37	137	47.4
NRTI+LPV/r 100/25mg regimen (tablet)	100	34	134	9.6
NRTI+ LPV/r 80/20mg liquid regimen (*)	100	272	372	9.7
NRTI+ LPV/r 40/10mg regimen (pellets)	100	467	--	5.2

[18] HIV/AIDS medicines and diagnostics service (AMDS) Global Price Reporting Mechanism (GPRM) http://apps.who.int/entity/hiv/amds/en/

[19] https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1

(*) the yearly cost of LPV/r liquid is higher than reported in GPRM, because we assumed that only 168 ml of a 300 ml bottle will be used, as the shelf life of an opened bottle is only 42 days.

Life years gained

According to a cost-effectiveness analysis by Cianarello et al.[20], the number of life years gained by using an LPV/r based first line (likely liquid formulation as only children less than 2 years of age at the start of treatment were included, and not LPV/r pellets as this analysis was published prior to 2015) instead of nevirapine based as a first line regimen was 1.2 years.

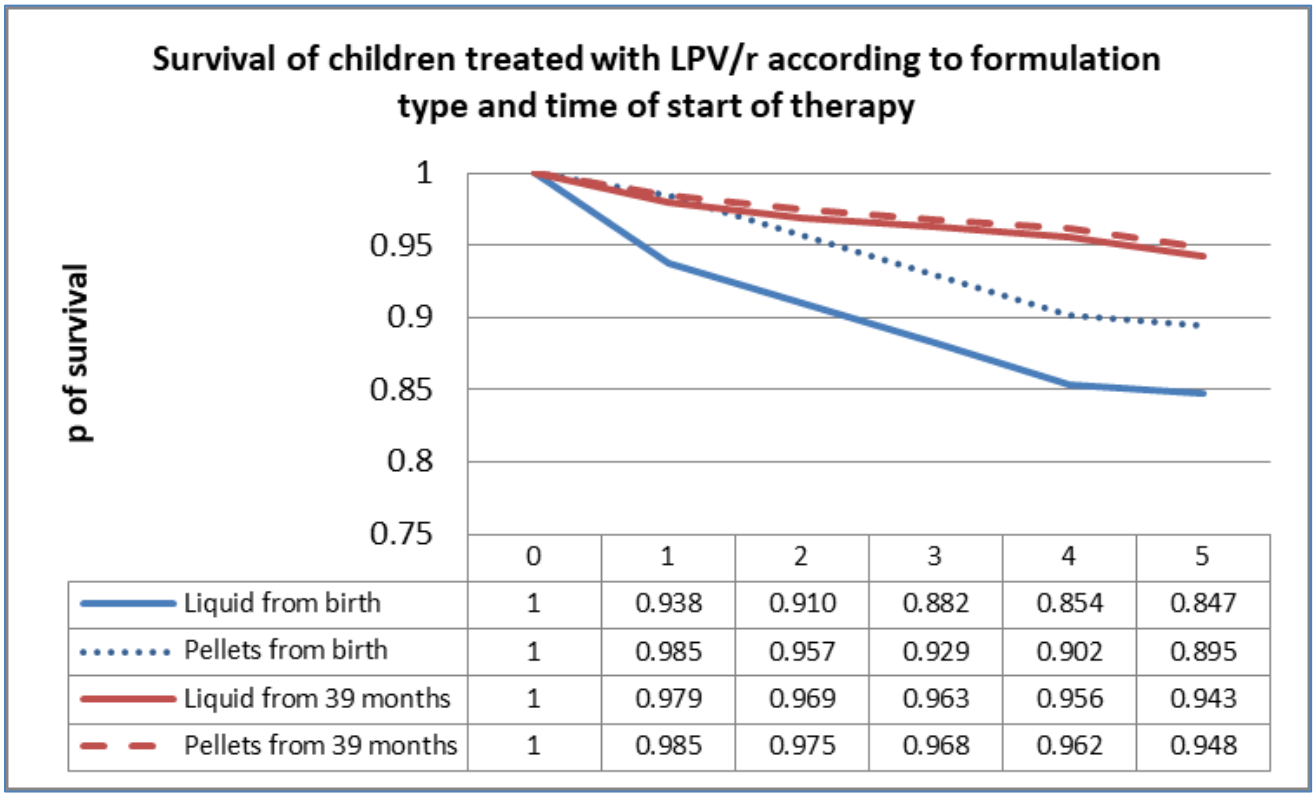
To assess whether switching from liquid LPV/r to pellets was associated with survival benefits the survival reported from the LIVING study up to week 48 was compared with the survival experience of LPV/r treated children in the paper by Cianarello et al.

Comparing the survival experience of children starting treatment at birth (time 0) and at the age of 39 months (the average age of entry into the LIVING study). The results obtained are shown in Figure 1 and Figure 2.

In figure1, the probability of survival is plotted against the age (in years) of children taking either LPV/r liquid formulation or the 2-in-1 pellets.

Please see annex 5 for a full methodology

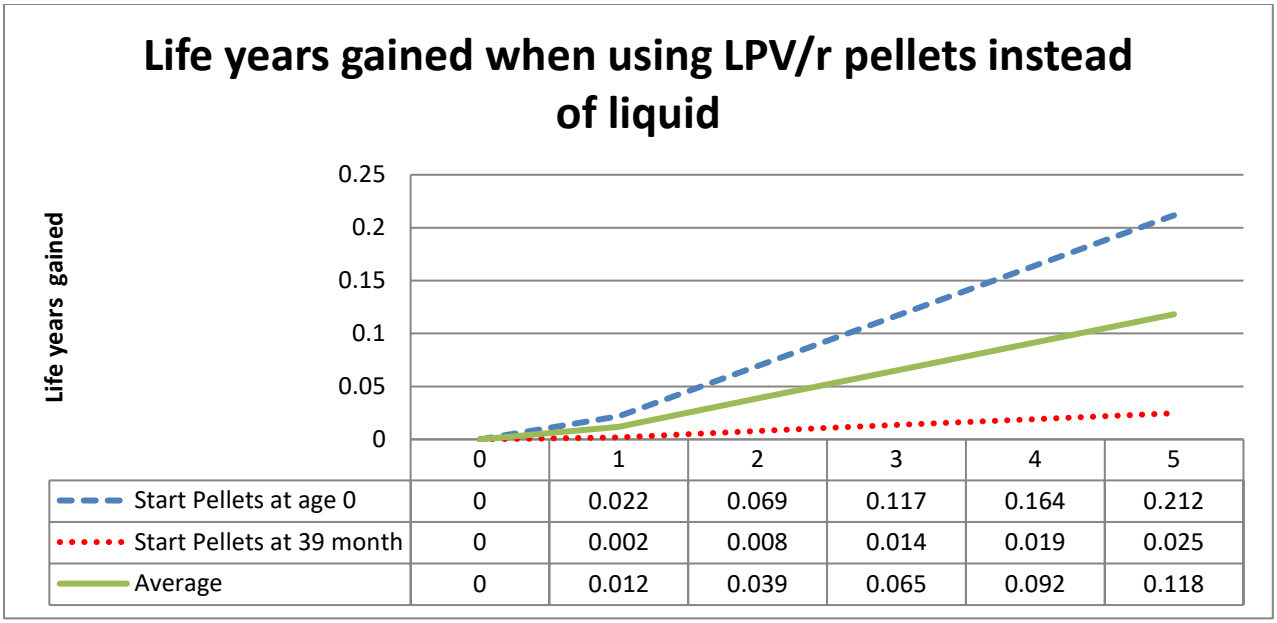
Figure 1:



	0	1	2	3	4	5
Liquid from birth	1	0.938	0.910	0.882	0.854	0.847
Pellets from birth	1	0.985	0.957	0.929	0.902	0.895
Liquid from 39 months	1	0.979	0.969	0.963	0.956	0.943
Pellets from 39 months	1	0.985	0.975	0.968	0.962	0.948

[20] Ciaranello et al, Cost-effectiveness of first line antiretroviral therapy for HIV-infected African children less than 3 years of age, in AIDS2015, 29: 1247-1259.

Figure 2:



	0	1	2	3	4	5
Start Pellets at age 0	0	0.022	0.069	0.117	0.164	0.212
Start Pellets at 39 month	0	0.002	0.008	0.014	0.019	0.025
Average	0	0.012	0.039	0.065	0.092	0.118

Results

Taking into account what countries procured for 2017, incremental cost-effectiveness based on what the eight countries procured was calculated as:

- In keeping with assumptions communicated to the evaluators by DNDi, the cost of 4-in-1 is assumed to be the same as the current cost of 2-in-1, thus $467.20 per patient per treatment year
- The incremental cost of using 4-in-1 pellets instead of AZT+3TC+NVP (3 in 1) regimen is $467 - $72 = $395, for a life expectancy gain of 1.318 (1.2+0.118) life years, the incremental cost-effectiveness of switching from AZT+3TC+NVP is $300 per life year gained
- The incremental cost-effectiveness of switching from 2NRTI +NVP 50mg regimen was calculated as $232 per life year gained.
- The incremental cost-effectiveness of switching from 2NRTI +NVP 10mg/ml regimen was calculated as $206 per life year gained
- The incremental cost-effectiveness of switching from 2NRTI +EFV 200mg regimen was calculated as $250 per life year gained
- The incremental cost-effectiveness of switching from 2NRTI+ LPV/r 80/20mg liquid regimen was calculated as $805 per life year gained
- 5.2% of children in the eight countries are already using 2-in-1 pellets, thus there are no additional benefits for them. Please see results in table 5 below:

The incremental cost-effectiveness for switching from standard of care treatment to 4-in-1 could arguably be improved if one takes into account the cost of treating opportunistic infections, which are reported to be less for children on 4-in-1. There may also be system savings in switching from LPV/r syrup. These factors were not included in this analysis due to lack of data.

Based on the composition of what the eight countries procured for 2017, (Table 4), switching the 2017 treatment population to 4-in-1 would have an incremental cost-effectiveness as follows:

Table 5: Incremental cost/life year of switching to 4-in-1 in the 8 countries.

Regime used in 2017	Proportion of children using the regimen in 2017	Increment in life expectancy from switch to 4-in-1	Incremental cost per year of the switch (USD)	Incremental cost effectiveness per life year gained (USD)
AZT+3TC+NVP (3 in 1) regimen	17.6%	1.318	395	**300**
2NRTI + NVP 50mg regimen	5.0%	1.318	306	**232**
2NRTI + NVP 10mg/ml regimen	5.5%	1.318	271	**206**
2NRTI+ EFV 200mg regimen	47.4%	1.318	330	**250**
2NRTI+ LPV/r 80/20mg liquid regimen	9.7%	0.118	95	**805**
2 NRTI + LPV/r pellets	5.2%	0	0	0

Switching from standard of care treatment to 4-in-1 would result in an incremental cost-effectiveness ranging from $206 per life year gained for children switched from 2NRTI + NVP 50mg regimen to $805 per life year gained for children switched from 2NRTI+ LPV/r 80/20mg liquid regimen.

An incremental cost-effectiveness of $300 or below ($300 because it is the highest value in the table above, if we do not include $805) would be considered cost-effective in all eight countries in the analysis except one, using gross domestic product, (GDP) income per capita of 2018, based on WHO-CHOICE threshold of less than three times the national per capita gross domestic product.[21] However, cost-effectiveness is only one measures of value for money, one would need to look at other factors surrounding the intervention.

The incremental cost-effectiveness is based on the assumption that the price of 4-in-1 will be equal to the current price of 2-in-1 or less when it is launched; should it be higher; the switch will become less cost- effective and price might become a barrier to the product adoption

[21] http://www.who.int/bulletin/volumes/93/2/14-138206/en/

2.4 Kenya Case Study

The evaluators visited Kenya to review in person the performance of the LIVING and RELIVING studies, visiting three very different sites. Firstly, the Kenyatta National Hospital site, the senior referral and teaching hospital in Kenya, in complete contrast the Lea Toto community site an informal housing area of Nairobi, and finally the PEPFAR-funded FACES site in Kisumu. DND*i* also arranged video conferences with their Ugandan and Tanzanian sites to discuss how the study had worked in their settings.

The LIVING study was conducted at twelve sites across Kenya, Uganda and Tanzania, this multi-site design worked well, and enabled generalised conclusions to be reached. A total of 1,003 patients were enrolled (Kenya 444, Tanzania 209, and Uganda 350). Around 16 percent of enrolled patients left the trial, the main reason for exiting the trial was relocation or change in family circumstances. No patient left the trial due to an adverse drug event.

Study results from all three countries confirmed that an ABC/3TC and LPV/r 40/10MG pellets regimen produced improved viral suppression in patients compared to LPV/r syrup and legacy regimens. The pellet formulation was generally well received by patients and caregivers as a significant improvement over the bitter tasting syrup.

The Principal Investigators, and their staff found the experience of the study to be rewarding and built in-country capacity. DND*i*'s management of the studies was well conducted, with positive support as monitors, mentors and colleagues to the sites and the Principal Investigators.

The acceptability of 2-in-1 pellets (used in the LIVING study) was reconfirmed by the short qualitative RELIVING study in interviews with caregivers at three sites in Kenya.

A wide range of different stakeholders, government offices, local NGOs and global NGOs were interviewed. DND*i*'s programme of advocacy and information sharing generated a strong demand for the 2-in-1 pellets, and potentially for the 4-in-1 granules. The advocacy was well managed and successful in informing countries, implementing agencies and global organisations of the development work on the 4-in-1 granules, and the availability of the 2-in-1 pellets in the interim. Information sharing on the 2-in-1 pellets supply situation was particularly difficult to manage due to the inconsistent messaging from Cipla Ltd.

The main challenge encountered was in the supply of the pellets in sufficient quantities to meet demand in the national programme encouraged by the positive study results. The USFDA approval of the 2-in-1 pellets, and WHO guidance elevating the ABC/3TC/LPV/r regimen to the preferred 1st line treatment led to several countries, including Kenya and Uganda, changing their guidelines, and beginning a process of transition. However, Cipla Ltd had only planned production capacity of up to 30,000 packs per month, far less than the total demand generated. Additionally, Cipla experienced a series of production difficulties, and supply did not reach even that level. The net result of this very difficult supply situation is that countries had to halt their transition to LPV/r pellets.

2.5 Results against Unitaid Key Performance Indicators

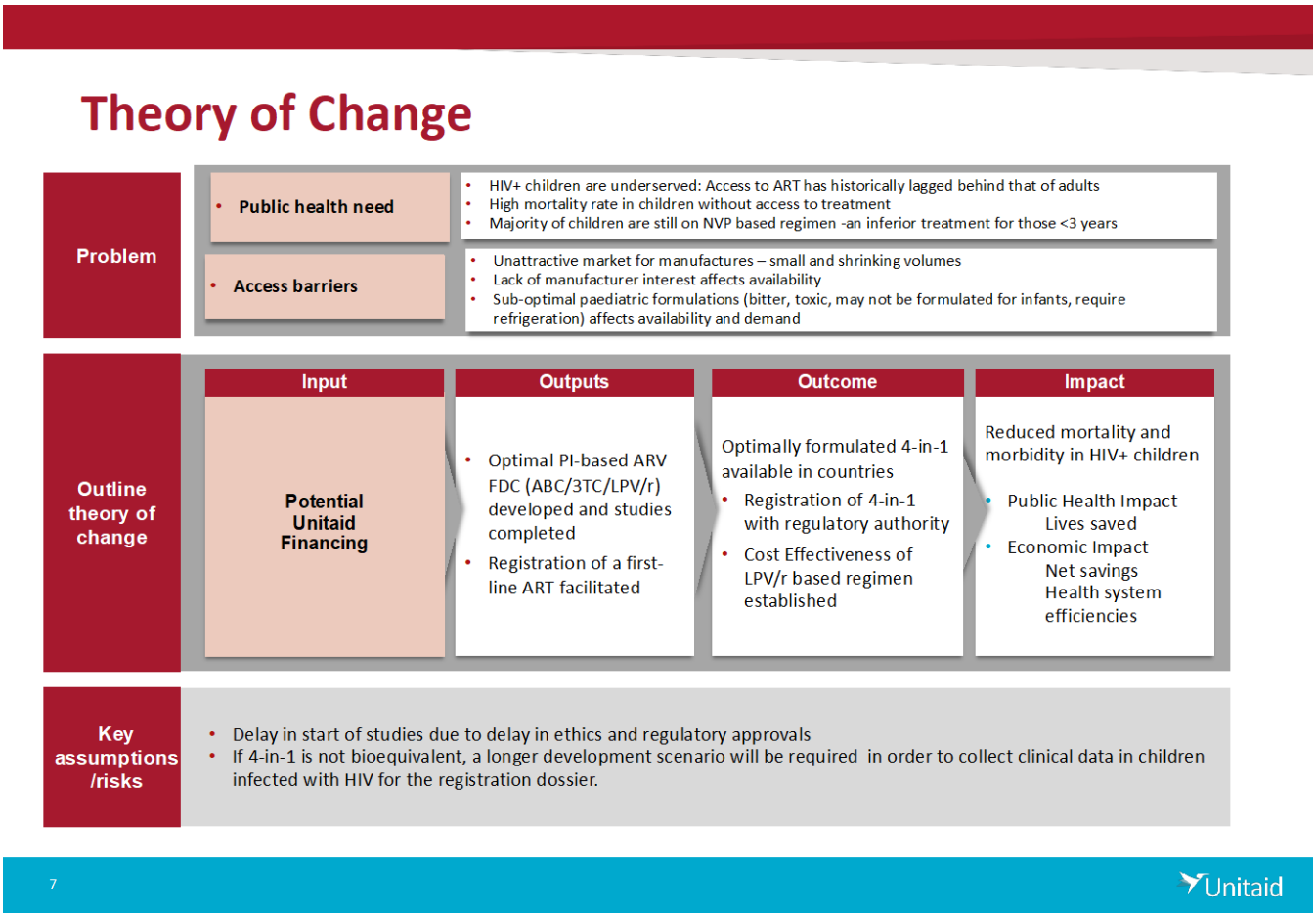
2.5.1 Unitaid's Strategic Key Performance Indicators

1-Catalyzing innovation	DND*i* and Cipla Ltd have developed one key optimal Paediatric ARV FDC (ABC/3TC/LPV/r) in granular form for use in young children under 3 years and/or under 25 KG who cannot swallow tablets. However, this novel product has not yet been approved by USFDA or WHO Pre-qualification, and therefore not yet available on the market. Production capacity levels have yet to be agreed with Cipla to ensure availability and supply security. See Section 2.2 on page 18 for a detailed description of achievements against this KPI
2-Overcoming market barriers	The LIVING studies have demonstrated that paediatric formulations in granular form for young children are highly acceptable to the patients and their caregivers. From the experience with the LPV/r 40/10MG pellets it is reasonable to anticipate a strong demand for granular products. However, the exact extent of demand and the longevity of the market are highly dependent on the speed of development and commercialization of DTG containing paediatric formulations. Results from the LIVING study confirm that an ABC/3TC and LPV/r 40/10MG pellets regimen produced improved viral suppression in patients compared to LPV/r syrup and legacy regimens. See Section 2.2 on page 18 for a detailed description of achievements against this KPI
3.1-Securing funding	Discussion with the major donors, and Government of Kenya indicate that donors and countries will follow WHO treatment guidance, even though this will result in higher cost per patient for the treatment drugs, compared to older less effective NNRTI containing regimens. The major donors indicated that funding will have to be made available from within existing budgets, but they expect to switch patients to the new products even though this may require some realignment of resources within the existing budgets. Funding can, therefore, be considered to be available.
3.2-Scaling-up coverage	Based on the intermediary scenario as the most likely uptake of the 4-in-1 when it becomes available, a total number of 19,512, [18,473-20,668] additional children would be in the treatment programs of the eight countries analysed for the two years 2020 and 2021. An increase of about 9% on treatment that can be attributed to switching to 4-in-1. Extrapolating this figure, which represents 48% of the treatment populations to a global level, based on the results these eight countries, an additional 41,146 children could be on treatment.

4.1-Increasing public health impact	Total number of life years gained in 2020 & 2021 would be 19, 861, [18,803-21,038] for the eight countries. Extrapolating this figure to a global level, based on the results of these eight countries, an additional 41,610 years could be gained, however, this figure is highly dependent on country circumstance, and considered to be a high estimate.
4.2-Generating efficiencies & savings	It is anticipated that the introduction of an FDC in granular form will occasion savings for logistics and dispensing services within national health systems, compared to the costs of storing, handling, distributing and dispensing LPV/r syrup. It is reasonable to assume that system costs and efficiencies will be similar to that experienced with legacy NNRTI containing regimens. However, in order to quantify such savings and efficiencies it would be necessary to have access to detailed system costings that separate out the costs of managing specific products, and activity costing within the national system. Accounting information to this level of detail is not unusually available from government systems and was not available to the evaluation team. It is also anticipated that there would be savings from reduced product wastage. The difficulties in maintaining the LPV/r syrup at the required temperature leads to a higher level of wastage than that experience with solid dosage forms. Clinicians interviewed during the evaluation also anticipate that improved adherence, reduced toxicity, fewer opportunistic infections, higher and more consistent levels of viral suppression from the 4-in-1 granular formulation will improve health outcomes for patients, resulting in programmatic savings for the health system. To accurately assess such savings would require a longitudinal research study to compare outcomes from the 4-in-1 granular formulation with those experienced in earlier regimens. However, in light of the now time-limited horizon during which this 4-in-1 presentation is the preferred 1st line treatment such research would be of limited value.
4.3-Delivering positive returns	A return on investment cannot be calculated at this time.

3 Conclusions and Recommendations

The Unitaid Theory of Change recognises the goals for the DND*i* Paediatric Grant as challenging. The key objective to create a 4-in-1 FDC required both a new 4 drug combination, but also in a granular form for very young children with taste-masking of the difficult LPV/r compound.



All research and development programmes are a journey into the unknown, the risk of bioequivalence was recognized in the theory of change and that has proved to be the most challenging element. The LIVING studies in Kenya, Tanzania and Uganda were successfully concluded, with only minor delays due to the obtaining ethics and regulatory approvals.

Overall the key objective of developing a child-friendly 4-in-1 formulation that can be administered to children that are unable to swallow pills has yet to be achieved. The desired FDC is now developed and has been submitted to USFDA for approval. At a meeting with CIPLA in December 2018, USFDA requested a further fasted-sate bioavailability study due to inconsistent results from the submitted study. Cipla are setting up a new study in quarter 2 of 2019. They expect to be able to present the results of this new study by September 2019. If this latest study is satisfactory, and accepted by USFDA, approved is anticipated by late 2019 or

early 2020. On this basis the evaluators assess that the earliest it can be expected that the product could be commercialised is by mid-2020.

3.1 Conclusions

3.1.1. Registration of the ABC/3TC/LPV/r as a fixed dose combination in a taste masked granular form has not been achieved.

Cipla and DND*i* are both hopeful that when the results of the additional studies planned for quarter 2 of 2019 are known, NDA product dossiers can be submitted to USFDA for approval, and thereafter to WHO PQ. When approved, in-country registration can begin, as the first step towards in-country adoption and transition or initiation of patients to the new product. Commencing transition at that time, mid-2020, will be approximately 4 years later than envisaged in the original Grant signed with DND*i* 2013.

3.1.2. The original timelines in the grant, and subsequent delivery estimates, have proved to be over optimistic

At the outset of the grant it was expected that a modular concept reduces drug development time allowing new drugs to be incorporated/exchanged with the current drug combination when new evidence supporting its use emerges. The individual ARVs i.e. LPV/r, 3TC and ABC are separate granules which could be replaced to incorporate new drugs where appropriate. In the original project plan this was expected to reduce drug development time as a flexible way of developing drugs. The degree of difficulty in taste-masking LPV/r and maintaining bioavailability in the granular form was under estimated. Numerous optional formulations, incorporating different excipients had to be tried before the current successful formulations was agreed upon. It was necessary to use a polymer for the hot melt extrusion for manufacture of the granules that had not been used before in this way. DND*i* advised the evaluators that even the producers of this polymer could not be certain how it would react or perform. With hindsight it is not surprising that milestones were missed with this degree of uncertainty in the research and development process.

However, with the knowledge of how challenging this process was likely to be, Cipla and DND*i* continued to give relatively short timelines in subsequent iterations of the project plan. There appeared to the evaluators to be an optimism bias in setting timelines, and a more detailed examination of remaining risks, and potential delays, when revising project plans could have tempered what proved to be optimistic targets.

Several interviewees in the evaluation process felt that realism in offering long time lines was overcome by the desire to see a much-improved product available for children living with HIV. A number of stakeholders advised the evaluators that the succession of missed deadlines had undermined faith in the development process, specifically estimates of when the product would be available for use by patients. This may reduce the commitment to introduce the formulation when it becomes available, particularly if development of paediatric forms of DTG-based regimens appear to be close to completion, registration and launch.

3.1.3. Development of ABC/3TC/LPV/r as a granular form FDC is still relevant for the treatment of paediatric patients, but now offers significantly less value than anticipated when the grant was designed

The combination of delays in development, and changes in the scientific landscape for the treatment of paediatric HIV have reduced the market value of this product. It is now anticipated that DTG-based formulations will become the 1st line treatment of choice in the foreseeable future. It is currently forecast that the first DTG-based granular format FDC could be on the market by 2022. If this date is achieved the window of opportunity within which 4-in-1 granules are the 1st line regimen of choice could be as short as 2 years. Thereafter, 4-in-1 granules will be an alternate 1st line treatment for children for whom DTG formulations are not appropriate or successful, or as an alternate if there are insufficient supplies of the DTG formulations. Several generic manufacturing companies are actively developing DTG-based formulations. WHO has very recently confirmed the desired dosages (February 5, 2019 expression of interest published by WHO[22]).

3.1.4. The project design of a Product Development Partnership was not optimal for leverage research and development competition with the market

The structure of the grant to use DND*i,* a product development partnership, able to deliver a range of services needed to develop the required product, engage other stakeholders and conduct studies in LMICs is sound. The alternative of a direct agreement with a generic manufacturer is more restrictive, and only addresses the technical aspects of the product development. However, in this instance the desired 4-in-1 product has not yet been developed and registered for use. The agreement between DND*i* committed Cipla Ltd to development of a formulation that may otherwise have proved to be unattractive to the market affected the balance of power in the arrangement. However, it appears to have been difficult for DND*i* or Unitaid to exert leverage over Cipla to accelerate development.

Despite the theoretical lack of attraction of this market niche, other generic manufacturers invested in development programmes for 4-in-1 granules, albeit they started later than Cipla. In interviews the evaluators were told that the existence of the PDP grant was on balance a negative factor in their decision-making, but in light of the medical need they decided to go ahead. On this basis the evaluators consider that a process where more than one company was supported or otherwise incentivised to develop the desire formulation could have been achievable, and potentially more successful.

Several interviewees, not just competing companies, suggested alternative designs such as subsidies or other support to more than one company, after a competitive process; or the use of market-based incentives such as purchase volume guarantees or pricing support. Options include grants towards the development costs, indicative prices, and working with other agencies to indicate likely demand at launch of the product, e.g. via advance market commitments. This would enable companies to accurately estimate what they could expect to earn from a successful product development.

[22] https://extranet.who.int/prequal/sites/default/files/documents/EOI-HIV_February2019_0.pdf

It was also suggested Unitaid could look beyond the usual development partners when considering investments in drug research, for example to include alternative development approaches; and to be more probing in establishing prospective grantees skills needed for a successful development. As an example, two subject matter experts with experience of Contract Research Organisations(CROs) used by commercial drug developers suggested that CROs could be considered as they are more familiar with working to fixed budgets and firm deadlines. It is recognised that CROs only address part of the development process, but it is within that part of the process that some of the major delays in this grant have been experienced.

3.1.5. There was little evidence of robust plans for a rapid introduction of and transition to the ABC/3TC/LPV/r granules once USFDA and WHO PQ is achieved

At the closure of the grant there was no commitment from Cipla Ltd to the level of production planned, or agreement on the price. DND*i* is working with other international stakeholders to agree a global forecast for 4-in-1 but was not yet able to tell the evaluators what level of demand they forecast for the 4-in-1 granules. Before a forecast is agreed global level planning, and in-country transition plans cannot for formulated. Transition to new regimens or formulations, particularly in paediatric programmes, has historically taken up to 24 months. For such a long-anticipated product we would expect to see well formulated plans that could be activated quickly. The major donors and country government have confirmed that funding is available, so this should not be a barrier to implementation, although some reprogramming may be required.

DND*i* confirmed to the evaluators that they are committed to introducing the 4-in-1, even though the Unitaid grant may now be completed. They have secured some external funding commitments and will use their own resources as needed.

3.1.6. The projected impact of the introduction of the ABC/3TC/LPV/r granular formula is that up to an estimated 40,000 additional children could be on treatment by the end of 2021.

However, at this stage the health impact can only be estimated based on a set of assumptions about the speed of transition to the 4-in-1 granules, and the date from which competing treatments based on DTG containing formulations may enter the market. On this basis it is estimated that in the years 2020 and 2021 an additional 19,512, [18,473-20,668] children would be in the treatment programs in eight countries analyzed. An increase of about 9% on treatment that can be attributed to switching to 4-in-1. Extrapolating this figure, which represents 48% of the treatment populations to a global level, an additional 41,146 children could be on treatment.

3.1.7 The LIVING studies were well conducted and confirmed both the acceptability of granules/pellets as a presentation, and the improved clinical effectiveness of the ABC/3TC/LPV/r regimen in young children

The multi-site centre design of the studies worked well and enabled more generalised conclusions to be reached. The envisaged delays with ethics and regulatory clearances were encountered, but overcome in a reasonable time to allow the studies in Kenya and Uganda to begin as planned and be concluded by the end of the grant, but the delays in Tanzania mean that the study there has overrun the end of the grant.

The pellets were well accepted by the majority of patients and caregivers, there were no adverse events suffered by patients that were associated with the pellets. It can be confidently assumed that the same acceptability will apply with 4-in-1 granules. Strong demand for the pellets from

patients not included in the study was generated in the communities served by the clinics administering the studies.

The decision to use 2-in-1 pellets as LPV/r part of the regimen enabled the studies to proceed, even though a 4-in-1 FDC was not yet developed. However, the coincident timing of the start of the studies, with USFDA approval of the 2-in-1 pellet product, and WHO guidance elevating the ABC/3TC/LPV/r regimen to the preferred 1st line treatment led to some confusion in country. Several countries, including Kenya and Uganda, reacted to the WHO advice, and apparent availability of the pellets to change their guidelines, and begin a process of transition. However, Cipla had only planned production capacity of up to 30,000 packs per month, far less than the total demand. Additionally, Cipla experienced a series of production difficulties, and have not reliably produced to this level of capacity. Promises to increase production capacity have not been met. As a result, there is great frustration in the market, and at the global level, the ARV Procurement Working Group (APWG) has had to assume the role of supply market managers, coordinating supply and demand. Cipla continues to have difficulties in meeting their delivery promises.

Many interviewees did not realise that development of 2-in-1 pellets was not part of the DND*i* grant and have associated the LIVING study and DND*i* with the challenges. As a result, DND*i* have felt drawn into the trying to help solve the supply chain challenges, which is something beyond the scope of the grant, and generally outside their skill set and experience.

The net result of this very difficult supply situation is that countries have had to halt their transition to LPV/r pellets: this is likely to affect the transition to the 4-in-1 granules formula.

Capacity was built in the organisations undertaking the studies and, in the individuals, concerned, many of whom had not been involved in studies previously.

3.1.8 DND*i*'s programme of advocacy and information sharing was successful and well managed, generating a strong demand for both the 2-in-1 pellets and the 4-in-1 granules

The programme of advocacy was well managed and successful in informing countries, implementing agencies and global organisations of the development work on the 4-in-1 granules, and the availability of 2-in-1 pellets in the interim. Unfortunately, the delays in development of the 4-in-1, and the supply challenges with 2-in-1 pellets, meant that much of the enthusiasm for these products then had to be tempered, and managed to the changing circumstances. The supply situation with 2-in-1 pellets has been particularly difficult to manage in terms of information sharing for the reasons given in Conclusion 6, and elsewhere in this report.

Reporting out from the LIVING study has been generally well handled, with mix of DND*i*'s corporate publications and briefings, and more formal peer-reviewed abstracts and presentations at conferences. Some interviewees felt that practical information from the studies that would be useful to clinics, and caregivers, could have been shared earlier with implementers, and the study sites.

3.2 Recommendations

3.2.1. Recommendations to Unitaid

3.2.1.1 Grant design should leverage the competitive dynamics within the market

The decision to base development on a single commercial development partner had the benefit of focusing effort, and possibly recognizing the limited attractions of the paediatric treatment, it did not prove successful in developing the product to the timetable required to maximise the advantages of developing this product.

It is recommended that future product development grants should, where feasible, support more than one company to generate competition both in the development process, as each will be keen to gain first mover advantage, and support market competition and supply security, even within smaller volume products, once the products are developed and on the market. At the time the grant was designed it was thought that a new paediatric product would not be attractive to multiple generic companies. In practice, for this product, which was envisaged as a new primary 1st line treatment, this did not prove to be the case, with two other companies launching their own development programmes. Options include grants towards the development costs, guaranteed prices, and volume guarantees for an initial period. Purchase volume guarantees and price targets will enable companies to more easily estimate what they could expect to earn from a successful product development.

The fact that other companies have gone ahead and developed granular options of the LPV/r 40/10mg 2-in-1 product suggests, that despite the small market size, companies, in the right circumstances, and with appropriate incentives, are prepared to invest in development of paediatric treatment products. It is, however, recognised that for very niche products, e.g. 2nd line or salvage regimens for paediatric patients, a single supplier route may be the only option.

Ensure that the grant requirements include a robust introduction and implementation plan for the product once developed and approved or be linked to other investments/grants that will support early introduction and implementation plans[23]. It is insufficient to develop the product, and then assume it will be taken up as envisaged. This will include forecasting of demand, a phased introduction that matches managing demand to available production as it ramps up, implementation tools and guides to national programmes, and other implementers. An active advocacy and advice programme for the post product development period will also be required.

There should also be a clear cut-off mechanism for when the grantee should pull back to allow normal mechanisms to take over.

3.2.1.2. Always select the commercial development partners via a competitive process

The selection of Cipla was made at the recommendation of the grantee based on their existing relations from developing a malaria product, and Cipla's experience in developing other paediatric products. In future all eligible generic manufacturers and other options should be considered in a competitive process to select the company/ies to be supported. The competition could also consider alternative development processes used by innovator, generic companies and

[23] It is noted that this has been added to the grant.

others in the pharmaceutical market. As an example, two subject matter experts suggested that Contract Research Organisations (CROs) could be considered as they are more familiar with working to fixed budgets and firm deadlines. It is recognised that CROs only address part of the development process, but it is within that part of the process that some of the major delays in this grant have been experienced.

3.2.1.3. Compete, or otherwise test, the selection of the grantee to ensure the grantee has the full set of skills and experience necessary to manage the grant

Ensure that the grantee has the full set of skills available, either in-house, via a wider consortium or in cooperation with other stakeholders[24]. Several interviewees questioned whether, as an R&D organization, DND*i* had the skill set and experience for the introduction of new products after development, specifically skills in transition to new products, forecasting and demand, and management of the supply market to ensure supply security. Such skills may exist within other active Unitaid grants. It is recognized that DND*i* is an active participant in many international working groups and treatment optimization partnerships to bring new products to patients and has access to a wide range of capabilities within these groupings.

It was also suggested that Unitaid could take a stronger leadership role in bringing different grantee together when they are operating in the same development and implementation space. The objective being to leverage the best skills sets across different providers.

3.2.1.4 Maintain flexibility in the grant design and implementation

By definition the full range of challenges in a research and development programme are unknown at the outset. It is therefore essential that the development programme can flex as circumstance change[25]. The programme should include clear development milestones at which progress can be judged, and as necessary the direction of the programme may change, including extending timelines by deliberate decision, not just in reaction to circumstances. More frequent and detailed development milestones may support earlier action to course correct, rather than finding out further down the line that targets have been missed. The design should include the clear option to allow for cessation of the programme, if circumstances are such that it will not be possible to meet the grant health impact objectives of the grant within time and budget.

The contracts between the grantee and the commercial partner responsible for development must include clear milestones that reflect the development milestones, with consequences, remedies and as appropriate, penalties for poor performance, and missed milestones. The majority of interviewees felt that there could be greater accountability from Cipla in this grant, and in the delayed deliveries of the 2-in-1 product.

3.2.1.5. An increased focus on risk management, scenario planning and risk mitigation in grant design

Although two risks were identified in the Theory of Change, one of which was the major factor in the extensive development delays experienced, it does not appear that DND*i* or Cipla actively managed risks, or robustly explored the impact of different potential delays. It is recommended

[24] This comment reflects statements made by several stakeholders interviewed. It is understood that this is now part of Unitaid's new operating model.
[25] This is also recognised in Unitaid's new operating model.

that grantees be required to prepare a rigorous risk profile based on the well-tried system of assessing Likelihood and Impact of each risk. From this profile the different risks should be plotted against the project plan to identify causal chains, and thus the impact of individual risks to the overall project timetable, and indeed the achievability of the objectives.

The risk profile and causal chains should be revisited at 6-monthly intervals, or at major events/challenges in the programme.

3.2.2. Recommendations to grantee

3.2.2.1. Early agreement on pricing and production capacity is urgent to support a successful introduction of the ABC/3TC/LPV/r granules

To enable countries, funders and implementing agencies to plan their transitions to the new 4-in-1 product it is essential that they know the costs and the timescale against which they can plan. At this stage the production plan can only be on the basis of Month 1 etc., as exact dates will only be available once USFDA approval is granted.

3.2.2.2. Prepare a new advocacy and advice programme ready for the launch of the ABC/3TC/LPV/r granules after approval by USFDA

It will be necessary to refresh the advocacy information on the product, the health and clinical advantages, and the high level of acceptability of the product by patients and their caregivers, previously issued, and to reassure countries on the supply security of the new product. Countries, and funders need to be confident the supply challenges experienced with the 2-in-1 pellets will not be repeated. This programme of advocacy and advice should include tools and implementation guides for transition for use down to the clinic level. The implementation guides and tools can be developed in cooperation with other stakeholders experienced in this work.

Annexes

Annex 1 -Acknowledgements

Procela Partners wish to acknowledge and thank all those who cooperated with us in the compilation of this Report, in particular

APWG	Wesley Kreft,
Cipla, India,	Vaishali Shridhankar, Dr.Shrinivas Purandare,
DND*i*	Bernard Pecoul, Ms. Annette Mahon, Ms. Janice Lee, Jean-René Kiechel, Dr Monique Wasunna, Dr Olawale Salami,
Faces Clinic, Kisumu	Dr Patriicl Oyaro
GFATM	Martin Auton
Ifakara Clinic Tanzania	Dr Maja Weisser and Dr Ezekiel Luoyang,
JCRC Uganda	Dr Cissy M Kityo,
KEMSA Kenya	Dr John Kabuchi
Kenyatta Hospital,	Prof Elizabeth Obimbo
Lea Toto LIVING Study	Sister Mary Owens, Daniel Karanja, Prof Rachel Musoke
MOH Kenya	Dr Laura Onyango, Dr Lydia Tuitai
Mylan	Anil Soni, Director, Kedar Madhekar & Prashant Sisodia
Unitaid Geneva	Ms. Gauri Khanna, Ms. Tijana Dragicevic, Ms. Sara Padidar
USAID	Dr Christine Malati
WHO	Dr Martina Pennazato,

We also thank other stakeholders from CHAI, EGPAF, ICAP, IAS, MSF, and NEPHAK Nairobi who gave of their time willingly for telephone or in person discussions.

Annex 2 -TERMS OF REFERENCE

Market Entry of Improved Protease Inhibitor Based Fixed-Dose Combinations for Children with HIV/AIDS End of Grant Evaluation

Purpose of These Terms of Reference

These Terms of Reference (TOR) serve as an overall framework for the services to be provided under this project.

Desired Timeframe
Requested start date: 7 January 2019
Expected completion date: 7 March 2019

1. Background
One child becoming infected with HIV or one child dying of AIDS is one too many1
Historically, children and infants have remained an underserved population with access to ART treatment trailing behind adults although the gap is narrowing. In 20172, 52% (37% – 70%) of children (0 – 14 years) had access to ART; in adults this figure was 59% (44% - 73%).

Major impediments to treating paediatric HIV has to do with the small market size and consequent lack of manufacturer interest and with the formulations themselves (bitter, toxic, can require refrigeration, may not be formulated for infants) resulting in low adherence in children. This critical shortcoming necessitates the need to find child appropriate drugs that can be used in resource limited settings with varied socio-economic contexts

In 2013, the Unitaid Executive Board committed up to US$ 17.3 million to the Drugs for Neglected Tropical Disease initiative (DNDi) to support the development of an appropriate paediatric HIV drug (henceforth the DNDi Paediatric HIV grant).

2. Objective of the DNDi Paediatric HIV grant
Unitaid funded DNDi to develop a new formulation containing a full antiretroviral regimen in an adequate formulation for children who cannot yet swallow tablets; in particular, two Fixed Dose Combination (FDCs) of the WHO-recommended first-line protease inhibitor-based regimen. In addition, the project aimed to develop a similar adapted formulation of a standalone PK booster (ritonavir) for children co-infected with TB/HIV.
In the absence of such formulations, countries were still either using substandard regimens (e.g. Nevirapine-based treatment despite increased resistance) or substandard formulations (e.g**.** protease-inhibitors syrups). Development of new child-friendly formulations in soluble granules would lead to the introduction of a new model for administration of medicines to infants and young children wo cannot swallow.
DNDi contracted Cipla, the India based generic manufacturer, to develop the novel formulations. Following significant scientific and technical delays early in the grant, DNDi and Cipla focused their efforts on one of the two FDCs; in 2016, CIPLA developed a 4-in-1 taste-masked lopinavir/ritonavir (LPV/r)-based fixed-dose combination.

Research studies

As a pathway to demand and adoption, DNDi is conducting the LIVING study in three countries – Kenya, Tanzania and Uganda – to evaluate the safety, efficacy, acceptability and adherence of a novel 2-in-1 formulation (LPV/r pellets), produced by Cipla. This study was completed in Kenya and Uganda in 2018 and is due to be completed in April 2019 in Tanzania.

DNDi also conducted the RE-LIVING study - an **in-depth** qualitative evaluation of adherence and acceptability of the novel 2-in-1 formulation (LPV/r pellets) – in Kenya which was completed in 2017.

Goal, Outcome and Outputs
Listed below is the goal, outcome and outputs that comprise the logical framework of this grant.
Goal/Impact: To make available optimal first line ART for young infants and children (defined as children who cannot swallow pills and are under the25kg weight band).
Outcome: Optimally formulated 4-in-1 available in endemic countries
Output 1: Formulate an optimal PI-based ARV FDC (ABC/3TC/LPV/r)
Output 2: Clinical studies initiated for 4-in-1 ARV/FDC (ABC/3TC/LPV/r)
Output 3: Registration of adapted paediatric ABC/3TC/LPV/r for use in resource-poor settings;
Output 4: Formulate a standalone PK Booster (RTV)
Output 5: Clinical studies completed for a stand-alone PK booster (RTV)
Output 6: Registration of an adapted paediatric RTV granules for use in resource-poor settings
Outputs 4, 5 and 6 were removed from the project plan in 2016, during the first no-cost-extension; there was no budgetary implementation under these outputs
Output 7: Facilitate the adoption of LPV/r based first-line ART and better adapted RTV formulation for super-boosting HIV/TB co-infected children in countries

3. Objectives of the Consultancy
Under this Terms of Reference (ToR), the evaluators will provide Unitaid with an assessment of the programmatic performance of the grant including on how successful it has been in bringing to market a child appropriate approved product by a WHO recognised regulatory agency that is available for procurement in resource limited countries. This will also include an assessment of the expected public health benefit and the economic impact.

4. Work to be performed
The evaluator is expected to perform an evaluation of the DNDi Paediatric HIV Grant with two main components:
1) An evaluation according to the Organisation for Economic Co-operation and Development's (OECD) Development Assistance Committee (DAC) standard evaluation criteria relevance, effectiveness, efficiency, impact, learning and risk mitigation (Annex 1) with an emphasis on lessons learned, grant impact and value for money. The assessment of the DAC criteria will require evaluators to consider some key aspects (internal and external) of the grant such as:
• Design of the grant
• Engagement with industry
• The emerging landscape for paediatric HIV treatment

It is expected that evaluators will critically review grant information and go beyond grant documentation and apply their analytical skills in the assessment of the DAC criteria.

2) An assessment of the grant performance against Unitaid's Key Performance Indicators
The DNDi Paediatric HIV grant was developed and implemented under Unitaid's first strategic period (2013-2016); it is closing in December 2018 which crosses into Unitaid's new and current strategic period (2017–2021). As such, the evaluator should put the grant into perspective of how the grant delivered against Unitaid's new Strategy (and Key Performance Indicators).

Unitaid's new strategy comprises nine Strategic KPIs that measure progress in delivering impact through investments made. They focus on the key moments that lead towards impact: from the point of closure of our grants, where innovation and access barriers are expected to be overcome (KPI 1 and KPI 2), to the scale-up of a new product (KPI 3) and its ultimate public health and health systems impact (KPI 4). While the KPIs apply to the whole portfolio of Unitaid, they are formally measured at the point of grant life when catalytic changes are meant to occur, and when adequate evidence is available: **typically,** at the time of grant closure.

Table 1: Unitaid's Strategic Key Performance Indicators

1- Catalyzing innovation	Total number of of Unitaid supported products for which product development activities have been successfully completed
2 – Overcoming market barriers	Total number of critical access barriers overcome during the strategic period
3.1 - Securing funding	Proportion of project countries where future funding has been secured at grant closure through partners and countries
3.2 - Scaling-up coverage	Additional number of people who benefit from a better health product.
4.1 - Increasing public health impact	Number of lives saved, and number of infections or cases averted
4.2 – Generating efficiencies & savings	Financial savings and health system efficiencies.
4.3 - Delivering positive returns	Return on investment

All strategic KPIs are in the scope of this evaluation – KPI 1, KPI 2, KPI 3.1, 3.2 and KPI 4.1, 4.2 and 4.34. A generic description of the KPIs are available at https://unitaid.org/assets/UTD18023_Report_KPI_proposal_022_WEB.pdf

For KPIs 1 and 2, the evaluator should evaluate and provide a substantiated assessment of whether the following critical access barriers have been addressed.

KPI 1: Innovation and availability
• KPI 2: Demand and Adoption
3 http://www.oecd.org/dac/evaluation/dcdndep/39119068.pdf

4For more information, refer to;
https://unitaid.org/assets/UTD18023_Report_KPI_proposal_022_WEB.pdf

For KPI 4, the evaluator is expected to provide estimates of potential impact under plausible assumptions using different roll out / adoption scenarios – while stating any limitation to the estimates. Evaluation of impact is expected on three fronts and should be based on quantitative methods:

• **Expected public health impact** – direct and short term for the LIVING study beneficiaries provided through the project but more importantly the indirect and long term impact from the expected roll out at scale of the 4-in-1 after grant closure and on approval by a WHO recognized regulatory agency in terms of expected increased patient access and additional lives saved against two alternate counterfactuals – the syrup-based regimen that was standard of care at the time the grant started and which has now been increasingly (though not entirely) replaced by the LPV/r pellets

• **Expected economic** impact from the 4-in-1 FDC developed under the grant agreement in terms of realized financial savings and health system efficiencies to countries

• **Return on investment** that requires a comparison of the expected benefits generated at scale with the anticipated costs / investments required to achieve these benefits

KPI 3: It is the aim of every Unitaid-funded project that access to the product supported is not limited to those served by the project but broadened to a wider population5. For this to happen, it is critical that funding is secured for the adoption at scale of a new treatment, a new technology or a new delivery mechanism. This requires strategic engagement with partners and countries during grant implementation on funding needs and to create the right conditions for scale up. With the conclusion of Unitaid's catalytic investment in the DNDi Paediatric HIV grant, evaluators are expected to assess the potential for securing funding for the 4-in-1 and the status of transition and scale-up: within this context, the effectiveness of partner engagement, in particular with large scale procurers, the ARVs Procurement Working Group and country regulatory agencies during grant implementation and the impact that this engagement has had on potential for adoption and roll out at scale.

4. **Target respondents** Target respondents would include (but are not limited to) the following:
• The lead grantee – DNDi – based in their Geneva office
• The lead manufacturer – CIPLA via teleconference in their India office
• In-country organisations/stakeholders in project countries involved with the DNDi grant or paediatric HIV treatment (including but not limited to policy makers / key decision makers at the county level, officials at relevant ministries)
a. Kenya
b. Uganda
c. Tanzania
• Wider stakeholder group indirectly involved with the Grant and involved in paediatric HIV treatment and care such as funders (e.g. GFATM, USAID, DFID, PEPFAR), technical agencies (e.g. CDC, WHO), regulatory authorities (e.g. SAHPRA, US FDA) other implementing agencies

working in the same space (e.g. EGPAF, CHAI, MSF), civil society groups, health care workers etc.
• Other manufacturers producing similar products to that of the DNDi-CIPLA 4-in-1. For example, Mylan, an India based generic manufacturer – that has produced the 2-in- 1 LPV/r granules
• Relevant staff at the Unitaid Secretariat
Unitaid's new Strategy comprises three strategic objectives; innovation, access and scalability. The generic definition of scale-up in the new Strategy is: the wide adoption and use of a product by the people who need it.
5. Place of work, method and frequency of interaction
Evaluators will work closely with the Unitaid Secretariat to undertake a review of the grant using grant documents, evaluation checklists, questionnaires and other related tools. The work will involve a desk-based review and qualitative interviews.
Evaluators will work remotely and may be required to travel to up to two project countries (e.g. Kenya and Uganda). Evaluators will also be expected to discuss with the Unitaid team in Geneva for the purpose of the evaluation at time of project kick-off (virtually or meet in person) and for presentation of the final findings (in person). In addition, the Unitaid focal point for the evaluation will have weekly to bi-weekly updates with evaluators. DNDi offices are based in Geneva and the evaluators could choose to either meet in Geneva or conduct interviews via virtual media.

6. Qualification and skills
Evaluators will have prior experience in designing and leading evaluations, pharmaceutical product development, impact analysis skills and technical competence in the field of Paediatric HIV treatment.
Specific expertise in the following areas would be essential:
• Experience and knowledge in working with pharmaceutical product development, and product approval processes through (stringent) regulatory agencies;
• Experience with value for money and impact assessment;
• Experience in monitoring and evaluation in low and middle-income country public health sectors;
• Familiarity with HIV (paediatric) treatment guidelines
• Proficiency in English
7. Deliverables
The contractor should submit the following deliverables by the dates determined for each evaluation:
Deliverable
Time
1. An Inception report outlining the process and work-plan for the evaluation;
1-2 weeks after signing of agreement
2. A draft evaluation report;
5 - 6 weeks after signing of agreement
3. A final evaluation report;
7 - 8 weeks after signing of agreement
The evaluation reports will be widely disseminated and available to all Unitaid Stakeholders, including the general public via Unitaid's website (www.unitaid.org).

8. Budget

All firms bidding are expected to submit their proposed budget, which will be discussed with the successful firm.

Payment Terms and schedule

For professional fees, payment will be made following satisfactory completion of the ToR and of corresponding detailed invoices indicating number of days worked per team member and deliverables

For travel costs, payment will be made in accordance with WHO rates and upon submission of invoices indicating actual travel costs with proof of payment. Evaluators are responsible to organize all logistics of travel, including hotel booking and local transportation.

UNITAID's Evaluation Framework

Relevance:

1. Are the outcome(s) and impact(s) of the grant aligned with Unitaid's overall mission to contribute to the scale up of and access to treatment for HIV/AIDS, malaria and TB for the most disadvantaged populations in developing countries using innovative global **market-based** approaches?
2. How did the grant contribute to Unitaid's strategy 2017 – 2021? (https://unitaid.org/assets/Unitaid-strategy-2017-2021_Dec-2017.pdf)

Effectiveness:

1. Are the outputs of the grant consistent with the objectives and expected outcomes as described in the project plan? If changes have been made, has the Unitaid Secretariat been involved in discussions and decision making on the changes?
2. Were the outputs of the project for the evaluation period fully achieved within the timeframe and budget specified in the initial project plan?
3. What are the main factors influencing the achievement or non-achievement of the outputs or overall outcomes?
4. What factors have been considered to ensure that value for money has been achieved?

Efficiency:

1. Have the grant implementer and co-implementer collaborated with national authorities in project planning, implementation and assessment?
2. How cost efficient and cost effective was grant implementation?
3. Were challenges raised with the Unitaid Secretariat in a timely manner and did the Secretariat participate in resolving these challenges?
4. Was the grant's procurement model designed to identify and solve procurement-related problems (where applicable)?
5. Were there any concerns or reported instances related to potential diversion of products, counterfeit products or **poor-quality** products?

Impact:

1. Has the grantee been able to report on impact as originally framed in the project plan and Log-Frame? If not, has the grant impact been measured in another way?
2. Where relevant, can the grantee attribute Unitaid's financial support for medicines, diagnostics or preventive products purchased to patients tested or treated in each beneficiary country?

Learning & Risk mitigation:

1. Have lessons learnt been documented and widely disseminated by grantees and Unitaid?

2. Have programmatic and financial risks been identified and tracked over the course of grant implementation?
3. Have the findings and recommendations of audits (where relevant) been used to improve grant performance?

Annex 3 -Unitaid Evaluation Framework

Relevance:
1. Are the outcome(s) and impact(s) of the grant aligned with Unitaid's overall mission to contribute to the scale up of and access to treatment for HIV/AIDS, malaria and TB for the most disadvantaged populations in developing countries using innovative global market based approaches? 2. How did the grant contribute to Unitaid's strategy 2017 – 2021? (https://unitaid.org/assets/Unitaid-strategy-2017-2021_Dec-2017.pdf)
Effectiveness:
1. Are the outputs of the grant consistent with the objectives and expected outcomes as described in the project plan? If changes have been made, has the Unitaid Secretariat been involved in discussions and decision making on the changes? 2. Were the outputs of the project for the evaluation period fully achieved within the timeframe and budget specified in the initial project plan? 3. What are the main factors influencing the achievement or non-achievement of the outputs or overall outcomes? 4. What factors have been considered to ensure that value for money has been achieved?
Efficiency:
1. Have the grant implementer and co-implementer collaborated with national authorities in project planning, implementation and assessment? 2. How cost efficient and cost effective was grant implementation? 3. Were challenges raised with the Unitaid Secretariat in a timely manner and did the Secretariat participate in resolving these challenges? 4. Was the grant's procurement model designed to identify and solve procurement-related problems (where applicable)? 5. Were there any concerns or reported instances related to potential diversion of products, counterfeit products or poor quality products?
Impact:
1. Has the grantee been able to report on impact as originally framed in the project plan and Log-Frame? If not, has the grant impact been measured in another way? 2. Where relevant, can the grantee attribute Unitaid's financial support for medicines, diagnostics or preventive products purchased to patients tested or treated in each beneficiary country?
Learning & Risk mitigation:
1. Have lessons learnt been documented and widely disseminated by grantees and Unitaid? 2. Have programmatic and financial risks been identified and tracked over the course of grant implementation? 3. Have the findings and recommendations of audits (where relevant) been used to improve grant performance?

Annex 4 – Performance against OECD DAC criteria

Relevance: The aim of the grant at the time it was designed and launched was clearly relevant as it sought to overcome the barriers to effective treatment of very young HIV positive children created by the lack of a child-friendly fixed dose combination for the preferred 1st line treatment of ABC/3TC/LPV/r. In particular the grant sought to develop ABC/3TC/LPV/r (also known as 4-in-1) in a granular format that could be administered with milk or soft foods (e.g. porridge).

However, the successive delays in development, testing and approval of the product have progressively reduced the relevance of this product. The evaluators specifically asked stakeholders the question if they considered the product relevant at the time the grant was launched, in 2015 when the LPV/r 40/10mg pellets product was granted approval by USFDA.

The consensus opinion from stakeholders was that the relevance of developing the 4-in-1 has declined over time, primarily due to the increased focus on Dolutegravir as a preferred treatment replacing LPV/r. It is currently anticipated by the generic companies that a dolutegravir containing paediatric regimen may come to the market as early as 2022. The net effect of delays in development of the 4-in-1 and the advancement of when dolutegravir products become available is to narrow the window in which the 4-in-1 could be considered the treatment of choice to as little as 18-24 months before being replaced by dolutegravir.

Once ABC/3TC/DTG becomes established as a preferred dolutegravir-based fixed dose combination, and the period of transition is estimated as another 24 months, the 4-in-1 is expected to become an alternative 1st line niche product with significant lower demand in the market.

The other major element of the grant was the LIVING and RELIVING studies. The evaluators found mixed views in the stakeholders on the relevance of these studies. As the 4-in-1 was not available, and the 2-in-1 was switched into the study, some stakeholders felt that the LIVING study was a repeat of the CHAPAS 2 study and reinforced the conclusions of CHAPAS 2. However, LIVING was a larger study than CHAPAS 2 and covered more sites and countries and added to the body of knowledge around the effectiveness of ABC/3TC/LPV/r as a 1st line treatment for very young children.

The conclusions around acceptability of the pellet form was considered to be useful and relevant by the clinics administering the studies and gave confidence for switching patients to pellet or granular forms.

Effectiveness – The grant has been less effective than envisaged at the time of design and launch, primarily due to the delays in development, testing and approval of the 4-in-1 formulation. The majority of external stakeholders questioned the degree of accountability applied to Cipla Ltd as the developer and wondered what impact the delays had on Cipla Ltd if the grant and contract between DND*i* and Cipla contained the correct mix of incentive and penalty for timely performance.

Stakeholders experienced in procurement and supply chain, and the market dynamics of the ARV market questioned the grant design of the Product Development Partnership with a single company, albeit that the demand for any paediatric product is limited. Nonetheless, most

stakeholders who commented on this aspect of the design felt that there should have been at least two companies supported to maintain a competitive element. This position is borne out by the fact that Mylan and Hetero both embarked on development programmes for a 4-in-1 granules product. The Mylan product expected to be submitted to USFDA for approval in 2019. This experience would seem to support an amended conclusion, that although much smaller than the adult ARV market, the paediatric market for 1st line regimens is interesting enough for more than one company to be prepared to develop new products

The selection of Cipla Ltd as the commercial partner in the Product Development Partnership was based on the existing relationship between the company and DND*i,* rather than as the result of a competitive process. One interviewee suggested that the development delays may have been lessened if the selected company was experienced in the production of granules for other pharmaceutical products. A further suggestion, from two interviewees experienced in commercial development, was whether Unitaid or, Product Development Partners, should consider alternative approaches and development options used by industry in the development of new drugs, as alternatives to international development and health sector NGOs.

As a result of the grant design to deliver the new product through a Product Development Partnership approach with a single commercial partner, there appears to have been very limited engagement with the wider industry. This was probably a missed opportunity. The evaluators were also advised that it had been suggested to DND*i* and to Unitaid that to broaden the scope of the LIVING study selected sites in Tanzania and Zambia[26] could use the Mylan LPV/r granules product. Budget was included in the 2017 NCE for use of the Mylan product. This suggestion was not taken up due to timing, and concern over the cost. Redesign of the Tanzania study would have required resubmission to the Tanzania Ethics Committee, and the timing of availability of the Mylan product (Q3 2018) would have resulted in up to a 12-month delay in the study. This would have taken completion of the Tanzania LIVING Study significantly beyond the end of the grant. This is unfortunate as it could have strengthened further the results of the LIVING Study.

The effectiveness of the LIVING study was somewhat reduced by the use of ABC/3TC and the separate LPV/r pellets. The timing of the study coincided with the inclusion of LPV/r in the WHO treatment guidelines as the preferred 1st line treatment for young children, and the USFDA tentative approval of the LPV/r pellets. This caused some confusion in the three markets where the study took place with Kenya and Uganda adopting the LPV/r pellets in their national guidelines, and then not being able to get supplies due to the restricted capacity at Cipla, as discussed earlier. Meanwhile supplies were being ring-fenced for the LIVING study.

Nonetheless, the LIVING study was effectively run at its various sites. Data collection and analysis was centralized in Nairobi, and some PIs felt distanced from this process and not able to contribute to the analysis and conclusions which was closely controlled by DND*i*. There was also comment from some stakeholders external to the studies that results, and any key lessons or challenges experienced in the studies were slow to be shared with other who may benefit from the knowledge. It appeared to the evaluators that this comment may be a manifestation of the common tension between implementing agencies and national programmes who want to apply

[26] For practical reasons Zambia was not used in the LIVING study, focusing instead on Kenta, Uganda and Tanzania

new knowledge and be warned of risks at the earliest opportunity. Whereas the study managers and funders need to verify the results and analyses and may need to withhold conclusions for publication at appropriate gathering or in peer-reviewed journals.

Efficiency – The LIVING studies appear to have been well run and managed. Each of the sites visited by the evaluators said that the DND*i* monitors and the study manager and data centre staff had been supportive and well-informed. There was a need to adjust some of the protocols to adapt to local cultural needs or programme norms. For example, in Kenya the national protocol is a for one confirmatory test in 12 months before placing a child on treatment, rather than the two called for by the protocol, - this was amended. Also, there was a requirement to test RNA from a hair sample, but in Kenya it is normal that the first hair cutting is carried out by the paternal grandmother, - this was also removed. The local PIs felt that issues such as this and obtaining the local clearances would have benefited from the local PIs being involved earlier in the design of the studies to apply their local knowledge and use their networks.

A concern expressed by a number of stakeholders was the efficiency of DND*i*'s project management of Cipla and their development process. The evaluators discussed this with DND*i* and are satisfied that DND*i* did pursue a robust approach of bi-monthly in-person meeting with the Cipla development team, and followed up with regular emails and frequent phone calls. However, DND*i* reported that despite this regular pressure it was very difficult to keep Cipla to the commitments made in meetings, and timelines continued to slip. As discussed elsewhere in this report, the agreement with Cipla did not provide contractual leverage for DND*i* to use to enforce achievement of development milestones. Also, as said before, one has to keep in mind the uncertain nature of all research and development programmes.

Impact – at this stage, impact of the project can only be based on assumption of the impact of the 4-in-1 when it reaches the market. However, the evaluators did hear of several quantitative impacts as a result of the grant.

Several of the LIVING study sites had not undertaken clinical studies before, and all expressed great satisfaction from being involved, and from the mentoring and training they had received from DND*i*. Additionally, for several of the PIs this was their first experience as a PI, and even for one of the more experienced PIs this was the first time they had been involved in the drug trial at their location. In every case the organization, teams and individuals felt their technical capacity had been enhanced and they are keen to undertake more trials.

Quantitative analysis of impact is discussed in more detail in Section on page 28

Learning – In the design of the project the evaluators consider that the major lessons to learn are that in product development it is important to leverage the competitiveness that does exist even in the market for paediatric ARVs, and not focus on only one company.

In developing a new product of any type, it is important to assess the likely market at the outset, and to discuss production capacity and investment at an early stage with the company/ies involved. A rigorous and continuous risk profiling, mitigation and management is essential throughout the project.

The experience of the 2-in-1 supply challenges, convinces the evaluators that it is essential for the project design to include an estimation of demand for the prospective product. That

estimation should be revisited at least bi-annually, and whenever there is significant delay, or change in the product landscape. In this case the delays in development, and the advent of dolutegravir-based treatment protocols have both had a significant impact on the likely market for the proposed 4-in-1 product. During the time of evaluation DND*i* was working with the APWG, Global Fund, PEPFAR and others to agree a refreshed global forecast. This forecast is expected to be available during Q2 2019.

With regard to the LIVING study the major learning, as discussed above is that it is important to engage the in-country PIs and experienced trials/study staff at an earlier stage. Local expertise can support both the study or trial design to ensure it fits the country context and assist in obtaining national approvals in the most timely fashion.

A lesson from the LIVING study is that when Unitaid funds studies that can lead to licensing drugs for neglected diseases it is considered good practice to have multi-site studies, although more difficult, it makes results more generalizable.

Good monitoring is essential when planning to license the drugs, DND*i* provided a good level of monitoring for Uganda. Studies need to be rigorously monitored because USFDA might come to audit them unannounced, and sites need to be ready.

A further recommendation or learning from international stakeholders was whether too much was being expected of DND*i* in areas that are not their expertise. For example, in forecasting and demand management, regulatory affairs and supply chain management. There are many organizations, both commercial and NGOs that are specialists in these areas, who could be incorporated either as consortium member or via sub-contract. Alternatively, the evaluators are aware that Unitaid is supporting a number of grants in the paediatric and ARV market spaces, and a closer integration, or collaboration between grant-holders could produce a more efficient use of resources overall.

Risk Management – The evaluators are concerned that risk management of the grant has been very informal. With any research and development exercise there are many known and unknown risks to progress. It will never be possible to anticipate all potential risks, but we consider it should have been possible to develop a range of scenarios around various "what if" questions. Even if the exact cause of delay could not be envisaged, one could develop a chart on likelihood and severity of delay at different stages, or in different processes, and from that, assume a delay of 6 months, or 12 months, and then plot the impact of those estimated delays. To be robust such scenario planning will need to understand the interlinking of different aspects of the development process, and the wider project to construct a causal chain of reactions to the delays and periods of delay plotted.

Annex 5 -Approach and Methodology

5.1. General approach

The evaluation focused on the programmatic performance of the grant, including how successful it has been in bringing to market a child-appropriate approved product by a WHO recognized regulatory agency that is available for procurement in resource limited countries. This also included an assessment of the expected public health benefit and the economic impact, using the Unitaid Grant evaluation Framework. The achieved outcomes, outputs and activities required from the Grant were assessed against project goals, expected activities and outputs, and the contribution to meeting Unitaid's KPIs.

Additionally, the outcomes were assessed against the OECD/DAC evaluation guidelines, to report on the relevance, effectiveness, efficiency, impact and learning/risk mitigation efforts of the grant.

The evaluation comprised of four principal activities:

a) **Review of project documentation**, including project plans, contracts, progress reports, results and assessments by DND*i*
b) An extensive programme of **stakeholder interviews,** in person where practical, and otherwise by telephone or conference call
c) An **in-person visit to Kenya** by the Procela consultants to review the LIVING and RE-LIVING clinical trials of the LPV/r (2-in-1) pellets
d) **Assessment and analysis of the findings** from activities a), b) and c) to prepare the final report for presentation to Unitaid

5.2. Stakeholder Interviews

A major element of the evidence gathering for the evaluation was through an extensive programme of stakeholder interviews. See Appendix 6 for an alphabetic list of the interviews proposed.

The organizations and individuals interviewed fell into five broad categories:

- Directly involved organisations – Unitaid, DND*i* and Cipla
- Major international organisations, donors and normative agencies e.g. WHO, the Global Fund, PEPFAR, USAID
- International Non-Government Organisations e.g. Clinton Health Access Initiative, EGPAF, International AIDS Society
- National Governments and local Non-Government Organisations e.g. Ministry of Health, Kenya, JCRC, Uganda, NEPHAK, Kenya
- Other manufacturers e.g. Mylan, Hetero, ViiV

5.3 Impact Assessment Methodologies

Three scenarios were simulated, on the patient population of eight countries, Botswana, Kenya, Nigeria, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe, which are, based on UNICEF data[27], home to 48.7% of all incident paediatric HIV infections globally. These countries were

[27] For every child, HIV Epidemiology among children and adolescents, 2017; at: data.unicef.org

chosen based on burden of disease, development/income level, and level of mother to child transmission programs to achieve a representative mix. Scenarios are:

1) **Fast adoption, transition is very fast**

- Starting in 2020, 100% of all children initiating ART are started on 4-in-1
- Starting in 2020, 80% of children already on ART switch to 4-in-1 in the first year.
- *In 2022, 20% of all children initiating ART and 20% of all children already on ART are switched to DTG based regimen.*

2) **Middle course**

- Starting in 2020, 40% of all children initiating ART are started on 4-in-1
- Starting in 2020, 40% of children already on ART switch from standard care of treatment to 4-in-1. In subsequent years the same number of children already on ART is switched to 4-in-1, until 4-in-1 reaches a market share of 80%. This takes two years.
- *In 2022, 40% of all children initiating ART and 40% of all children already on ART are switched to DTG based regimen.*

3) **Conservative scenario (due to slow adoptions and supply side problems)**

- Starting in 2020, 20% of all children initiating ART will start 4-in-1
- Starting in 2020, 20% of children already on ART switch from standard care of treatment to 4-in-1 in year 1. In subsequent years the same number of children is switched to 4-in-1.
- *In 2022, 80% of all children initiating ART and 80% of all children already on ART are switched to a DTG based regimen.*

To each of the above scenarios, 3 different scenarios were applied to simulate the impact of the introduction of dolutegravir (DTG) on the treatment of children under< 5, under the assumption that it will become commercially available to treatment programs in 2022.

In the first part of the analysis we calculate the incremental number of children that would be retained on treatment due to better adherence, acceptability, and fewer lost to follow-up compared to the standard care of treatment. We use the retention rate which, for the LIVING study has been calculated at 90%. The 90% retention rate includes, acceptability, adherence, and mortality rates[28].

In the second part of the analysis we calculate the incremental cost effectiveness of 4-in-1 as opposed to standard of care treatment in the countries under consideration. The output is the incremental cost-effectiveness ratio (ICER) per life year gained, by switching to 4-in-1.

Part I

The number of children under 5 years of age in the treatment program was obtained, for 2019 up to 2024, by calculating the number of children starting ART retained in the treatment program from the years 2015, 2016, 2017, and the estimated number for 2018.

[28] DND*i* LIVING study data

The number of new cases in each year (2015 to 2018) was multiplied with the retention rate of 75% to yield the number retained the next year, the year after, and so on for 5 years.

Summing up the number retained in the program from the first to the 4th year after entering the program in previous years yielded estimates for the number of children under 5-year-old still in the treatment program, for 2019 up to 2024. For 2018, the number was assumed to be the arithmetic average of the number of children under 5 in years 2019 to 2024.

We consider that it is justified to proceed as described above to estimate the number of new cases entering the treatment program because, with the noteworthy exception of Nigeria, where rates are increasing, the uptake of ART appeared stable we considered it inappropriate to apply a linear extrapolation of the trends in different countries on the basis of three point estimates (2015, 2016 and 2017) only.

In the sensitivity analysis we assess whether increasing or decreasing the number of children starting treatment each year by 5% would have an effect on the outcome.

Results are presented in table 3 and table 6.

Table 6: Incremental life years gained by switching to 4-in-1 from standard of care treatment in 2020 and 2021 in the eight countries

Scenarios	Rate of adoption	Total number of life years gained 2020&2021
Fast track scenario	In 2020, 100% of all children initiating ART and 80% of children already on treatment switch to 4-in-1.	28,603 [26,753-30,587]
Middle course scenario	In 2020, 40% of all children initiating ART and 40% of children already on treatment switch to 4 in 1.	19,848 [18,536-21,259]
Conservative scenario	In 2020, 20% of all children starting treatment, 20% of existing children on treatment switch to 4 in 1.	9,924 [8,738-10,630]

Part II

In part II we calculate the incremental cost effectiveness of switching to 4-in-1 as opposed to standard of care treatments in the countries under consideration. The output is the incremental cost-effectiveness ratio (ICER) per life year gained.

The regimens used in the eight countries were inferred from their procurement behaviour in 2017 as reported in GPRM.[29]

[29] HIV/AIDS medicines and diagnostics service (AMDS) Global Price Reporting Mechanism (GPRM) http://apps.who.int/entity/hiv/amds/en/

Using guidelines from the weight-based dosing for ARV formulations for infants and children from WHO guidelines[30] , we calculated the cost of the NRTI component of different regimens as the cost of ABC+ 3TC 60/30 mg, ZDV+3TC 60/30 mg, ZDV 60 mg, ABC 60 mg, the latter 3 complemented with 3TC 10 mg/ml, weighed for the volume of the ABC and ZDV components) for a 12.7 kg infant, based on the GPRM data of 2017, because 12.7 kg was the median weight of children in the LIVING study. To this we added the cost of other formulations needed to make a full regimen, and thus its treatment cost per year. The results are shown in table 4 in the body of the report.

Life years gained

According to a cost effectiveness analysis by Cianarello et al.[31], the number of life years gained by using a LPV/r based first line (likely liquid formulation as only children less than 2 years of age at the start of treatment were included, and not LPV/r pellets as this analysis was published prior to 2015) instead of nevirapine based as a first line regimen was 1.2 years.

We assessed whether switching from liquid LPV/r to pellets was associated with survival benefits. To do so we compared the survival reported from the LIVING study up to week 48 with the survival experience of LPV/r treated children in the paper by Cianarello et al. The result compared survival experience of children starting treatment at birth (time 0) and at the age of 39 months (the average age of entry into the LIVING study).

The survival probabilities from the paper by Cianarello et al. were obtained by graphic back-calculation from the published survival curve. Any survival benefit apparent at the age of 48 weeks among children in the LIVING study was assumed to be definitively acquired and carried forward to the end of the 4th year of life (i.e. the 5th birthday).

While this method has obvious limitations in terms of accuracy, survival benefit was found in both assessments, which at the very least would seem plausible in view of the improved adherence and retention reported with 2-in-1 pellets as compared to liquid formulation. The results obtained are shown in Figure 1 and Figure 2 in the main body of the report.

We thus estimated the survival benefit associated and attributable to the use of LPV/r pellets over and above that of using LPV/r liquid formulation to be between 0.025 and 0.212 life years, over a period of 5 years, with a best estimate of 0.118 life years. We would not attribute more life year gains to the use of the 2-in-1 pellets, because beyond the age of 5 years children should be expected to be using other formulations. The result is a gain of 1.2 + 0.118 = 1.318 life years from the use of 2-in-1 pellets, compared to using standard of care treatment with a NVP based regimen.

We used the average of survival benefit in children starting at birth and starting at 39 months of age because the estimated survival benefit of starting LPV/r pellets at birth is likely an overestimate, as the LIVING cohort (which started enrolling at an average age of 39 months) would have a better survival than a cohort starting treatment at birth because of selection bias. This is used as the upper bound of the potential survival benefit nonetheless, because the intended used of the 2-in-1 pellets is in the 0 to 3 years of age population.

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[30] https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1

[31] Ciaranello et al., Cost-effectiveness of first line antiretroviral therapy for HIV-infected African children less than 3 years of age, in AIDS2015, 29: 1247-1259.

Annex 6 - Stakeholder Questions

All interviewees were asked for their general impressions of the programme, its achievements, known barriers, the level of their organization's involvement, and their engagement with DND*i*. Other questions were tailored to the organization and their category e.g.

a) Unitaid, DND*i* and Cipla received the most detailed questions on the management of the grant/programme, the barriers, delays, successes and future prospects. Cipla were asked about their motivation in developing the products, and their view of the benefits received from the Grant.
b) The international organisations were asked about their role in encouraging the development of the products, the product's position in recommended treatments, the likely impact of the introduction of dolutegravir-based regimens; and for the donors their commitment to funding procurement of the products.
c) International NGOs were asked about their level of engagement, their views on the suitability of the products, and their views on the likely usage and development of treatment protocols for paediatric patients.
d) The national organisations were asked about their level of engagement, specifically in relation to the LIVING and RELIVING studies, and expected usage of the products in `their countries.
e) The other manufacturers were asked about their production plans for similar or competing products, and whether the existence of the grant funded product development plan with Cipla encouraged or discouraged their company to develop their own products.

Annex 7 -Country Visit to DNDI Kenya

The primary purpose of the visit to Kenya was to review first-hand the LIVING and RE-LIVING clinical trials, including an examination of the data and other records, discussion of the challenges in recruiting patients, any delays encountered. Unitaid specifically requested Procela to form an opinion on the value received from the trials, as they were a major element of expenditure under the grant.

In judging the value of the trials Procela considered the fact that the trials were only conducted using the 2-in-1 LPV/r pellets, and not as envisaged in the grant design the 4-in-1 product. Unitaid also asked Procela to consider what added benefits have been generated through capacity building of the local organisations involved in running the trials. It was known that for some sites this was the first time they had run clinical trials.
The Procela team also met with appropriate Ministry of Health officials, and with KEMSA the government procurement and stores agency.

Annex 8 -List of Interviewees

Organisation	Interviewee(s)	In-person	Call	Video
ARV Procurement Working group	Wesley Kreft, WG Coordinator		✓	
Cipla Ltd, India	Vaishali Shridhankar, Regulatory Affairs Department Dr.Shrinivas Purandare, R&D Department & others		✓	
Clinton Health Access Initiative, New York	Carolyn Amole, Director, Access Programmes		✓	
Clinton Health Access Initiative, Nairobi Office	Davis Karambi, Access Programmes Justus Ogando, Regional Manager	✓		
DND*i* , Geneva	Bernard Pecoul, MD, MPH, Executive Director Ms. Annette Mahon, External Relations Manager Ms. Janice Lee, Senior manager for Access HIV Jean-René Kiechel, Snr Technical Adviser François Bompart, Director, Paediatric HIV/HCV Patricia Caldwell, Senior External Relations Manager	✓		
DND*i*, Kenya	Dr Monique Wasunna, Director Dr Olawale Salami, Clinical Project Manager Linet Otieno, Regional Communications Manager Simon Bolo, Regional Operations Leader Moses Waweru, Project Coordinator Raymond Omollo, Data Manager	✓		
EGPAF - Geneva	Assoc. Prof. Jennifer Cohen, Senior Director of Innovation		✓	
FACES Clinic, Kisumu - LIVING Study site	Dr Patrick Oyaro: Co-principal Investigator Moses Nondi : Clinical Officer and Study Coordinator Eunice Onyango: Research Assistant Dennis Kipngeno: Pharmacy Technician Brian Ondara: Laboratory Technologist	✓		
GFATM – HIV Dept	Requested via Unitaid, but no response			

GFATM – Procurement Team	Martin Auton, Supplier Relations, Pharmaceuticals		✓	
Hetero	Requested, but declined			
i-Base	Polly Clayden		✓	
ICAP, New York	Dr Nandita Sugandhi, Snr Adviser, Paediatric Treatment		✓	
Ifakara Clinic, Tanzania - LIVING Study site	Dr Maja Weisser and Dr Ezekiel Luoyang, Site PIs			✓
Int. AIDS Society, Geneva	Ms. Marissa Vicari, Paediatric Portfolio Industry Liaison		✓	
JCRC Uganda - LIVING Study site	Dr Cissy M. Kityo, Executive Director, and PI			✓
KEMSA, Kenya Medical Stores Agency, Nairobi	Dr John Kabuchi, Procurement Manager	✓		
Kenyatta National Hospital, - LIVING Study site	Prof Elizabeth Obimbo, Site PI, Dr. Caren Mburu, Site Paediatrician	✓		
Lea Toto (Children of God Relief Institute - LIVING Study site	Sister Mary Owens (Executive Director) Prof Rachel Musoke (Principal investigator Daniel Karanja (Study Coordinator) Dr Mario Paul (Study Medical Officer) Paul Mulongo (Lea Toto Program manager)	✓		
Macleods Pharmaceuticals Ltd, India	Requested, but declined			
Médecins Sans Frontières (MSF) – Geneva	Jessica Burry, External Relations		✓	
Ministry of Health, Kenya - National AIDS Control Programme - Pharmacy and Poisons Board	Dr Laura Onyango, Head of Paediatric Dept. NASCOP Dr Lydia Tuitai, Deputy Manager, Clinical Trials, PPB	✓ ✓		
Mylan Ltd	Anil Soni, Director Kedar Madhekar & Prashant Sisodia		✓	

National AIDS Control Commission, Nairobi	Joab Khasewa, Program Officer HIV Prevention	✓		
NEPHAK, (National Empowerment Network of People Living with HIV/AIDS in Kenya)	Nelson Juma Otwoma, Executive Director	✓		
Unitaid	Ms. Gauri Khanna, Ms. Tijana Dragicevic, Ms. Sara Padidar & Others	✓		
USAID	Dr Christine Malati, Snr Pharmacist, GHSC			✓
USFDA	Meeting requested and declined, information provided by Cipla Ltd.			
ViiV	Requested, but no response			
WHO – HIV Dept	Dr Martina Pennazato, Snr Adviser, Paediatric HIV		✓	
WHO Pre-qualification	Deleted as not required			

Annex 9 -Other Relevant Documents

9.1 Unitaid Standard Definitions of Market Barriers

	Definitions	Examples of interventions
Innovation & Availability	• Robust pipeline of new products • Evidence-supported, adapted products are rapidly introduced in markets	• *Drugs and tools development* • *Clinical evidence* • *Country registration*
Quality	• Product available at stringent standard of quality (incl. starting and intermediary materials), with accessible information	• *WHO products pre-qualification*
Affordability	• Product available at lowest price: sustainable for suppliers, and not unreasonable for governments, donors and patients	• *IP agreements* • *Incentives to manufacturers to enter markets*
Demand & adoption	• Countries, programmes, providers and end users rapidly introduce and adopt the most cost-effective products	• *Demand creation through social marketing*
Supply and delivery	• Supply chain systems (incl. quantification, procurement, storage, and distribution) function effectively, reliably and timely • Available and sustainable supply exist	• *Manufacturing process improvement* • *Supply chain excellence* • *Pilots for delivery models*

9.2 List of Scientific Publications for Paediatric HIV – DNDi

Lopinavir-ritonavir super-boosting in young HIV-infected children on rifampicin-based tuberculosis therapy compared with lopinavir-ritonavir without rifampicin: a pharmacokinetic modelling and clinical study by Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S, Liberty A, Simon F, McIlleron H, Cotton MF, Lallemant M. The Lancet HIV, January 2019
https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30293-5/fulltext

Assessing the adoption of lopinavir/ritonavir oral pellets for HIV-positive children in Zimbabwe by Pasipanodya B, Kuwengwa R, Prust ML, Stewart Christine B, Murimwa CT, Brophy J, Salami O, Mushavi A, Apollo T. Journal of the International AIDS Society, December 2018
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6293134/

Understanding the acceptability and adherence to paediatric antiretroviral treatment in the new formulation of pellets (LPV/r): The protocol of a realist evaluation by Giralt AN, Nöstlinger C, Lee J, Salami O, Lallemant M, Ouma O, Nyamongo I, Marchal B. BMJ Open, March 2017
https://bmjopen.bmj.com/content/7/3/e014528

An analysis of volumes, prices and pricing trends of the pediatric antiretroviral market in developing countries from 2004 to 2012 by Lee JSF, Teyssier LS, Nguimfack BD, Collins IJ, Lallemant M, Perriens J and Moatti JP., BMC Pediatrics, March 2016
https://www.ncbi.nlm.nih.gov/pubmed/26979974

Optimizing drugs to reach treatment targets for children and adolescents living with HIV by Penazzato P, Lee J, Capparelli E, Essajee S.M, Ford N, Ojoo A, Pascual F, Sugandhi N and Lallemant M. Journal of the International AIDS Society, December 2015
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4670841/ How can we end paediatric HIV? by Celletti F, Cohen J, Connor C, Lallemant M, Lee J., The Lancet HIV, March 2015
https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(15)00025-9/fulltext

Lopinavir/ritonavir plus lamivudine and abacavir or zidovudine dose ratios for paediatric fixed-dose combinations by Bouazza N, Foissac F, Fauchet F, Burger D, Kiechel JR, Treluyer JM, Capparelli EV, Lallemant M, Urien S. Antiviral Therapy, October 2014
https://www.ncbi.nlm.nih.gov/pubmed/25279808

The pharmacokinetics and acceptability of lopinavir/ritonavir minitab sprinkles, tablets and syrups in African HIV-infected children by Musiime V, Fillekes Q, Kekitiinwa A, Kendall L, Keishanyu R, Namuddu R, Young N, Opilo W, Lallemant M, Walker AS; Burger D, Gibb DM., JAIDS, March 2014
https://www.ncbi.nlm.nih.gov/pubmed/24828266

Pediatric HIV – A neglected disease? by Lallemant M, Chang S, Cohen R, and Pécoul R. The New England Journal of Medicine, August 2011
https://www.nejm.org/doi/full/10.1056/nejmp1107275

Presentations at Conferences for Paediatric HIV – DNDi – Dec. 2017 to present

Each year, one or a few members of DND*i*'s Paediatric HIV team attend several conferences to promote/share/present their work. The major relevant conferences in the HIV field are IAS, ICASA and CROI. • International Conference of HIV/AIDS and STIs in Africa (ICASA) – Dec. 9, 2017 (Ivory Coast) – poster presentation on LIVING Study; two presentations on LIVING Study by Victor Musiime, PI (see below).

Assessing acceptance and acceptability of an innovative pediatric antiretroviral lopinavir/ritonavir (LPV/r) pellet formulation

W. Onyango-Ouma[1], Christiana Nöstlinger[2], Bruno Marchal[2], Isaac Nyamongo[1], Olawale Salami[3], Marc Lallemant[3], Ariadna Nebot Giralt[3], Janice Lee[3]

[1] Institute of Anthropology, Gender and African Studies, University of Nairobi, Nairobi, Kenya.
[2] Department of Public Health, Institute of Tropical Medicine, Nationalestraat 155, Antwerp, Belgium.
Drugs for Neglected Diseases initiative, 15 Chemin Louis-Dunant, 1202 Geneva, Switzerland.

Background

- WHO (2015) recommends the use of a LPV/r based regimen for all children < 3 years of age.
- LPV/r formulation for infants and young children most widely available is a syrup that requires refrigeration, contains 40% alcohol and tastes bitter.
- Cipla's LPV/r pellets have a new solid formulation which does not require refrigeration; they were tentatively approved by USFDA in 2015 for children from 2 weeks or above 5 kg.
- However, no acceptability data is available.

- The LIVING clinical trial evaluates the effectiveness, pharmacokinetics and safety of this new formulation in Uganda, Kenya and Tanzania.
- In order to scale up the use of these pellets at national program level, DNDi commissioned a theory-driven realist evaluation (RE-LIVING study).
- The RE-LIVING study aims to better understand how the pellets are used in real-life settings.

Objective

To assess the formulation's acceptability and adherence from the perspective of the child, caregiver, and healthcare providers, and to explore which caregiver, organizational, and contextual factors facilitate acceptance and adherence to this new formula.

Methods

Qualitative research (participants and settings)
- Cases: dyad caregiver-infant (purposively selected)
- Three contrasting units of analysis (settings): Kenyatta National Hospital and Gertrude's Children's Hospital in Nairobi, and Lumumba clinic in Kisumu

Data collection (January – June 2017)
- 42 in-depth interviews with care-givers and 16 with health care providers
- 17 observations of pellet administration at home and 17 in clinical settings

Data analysis (June – November 2017)
- Primary analysis (qualitative descriptive) inductively conducted
- Secondary analysis (realist analytical) deductive-inductively conducted
- Data triangulation (theoretical, data sources, and investigator triangulation)

Results

Acceptability

Caregivers found the pellets highly acceptable due to
- the ease of storage (no refrigeration required)
- the packaging (discreet, secure closing, no spillage)
- administration with liquids
- taste: lack of bitterness

Children accepted the treatment pellets very well
- Easy to swallow when given with liquids or food

Adherence

- Better acceptability of the new formula contributes to initiation of adherence.
- Visible positive outcomes of giving the new formula (such as less viral load or gaining weight) stimulates maintaining adherence.
- Easy administration empowers caregivers and therefore supports their adherence to the treatment.
- Adherence support (counseling) delivered within the trial was highly appreciated, though instructions need to be adapted to the caregivers' level of understanding.

Conclusions

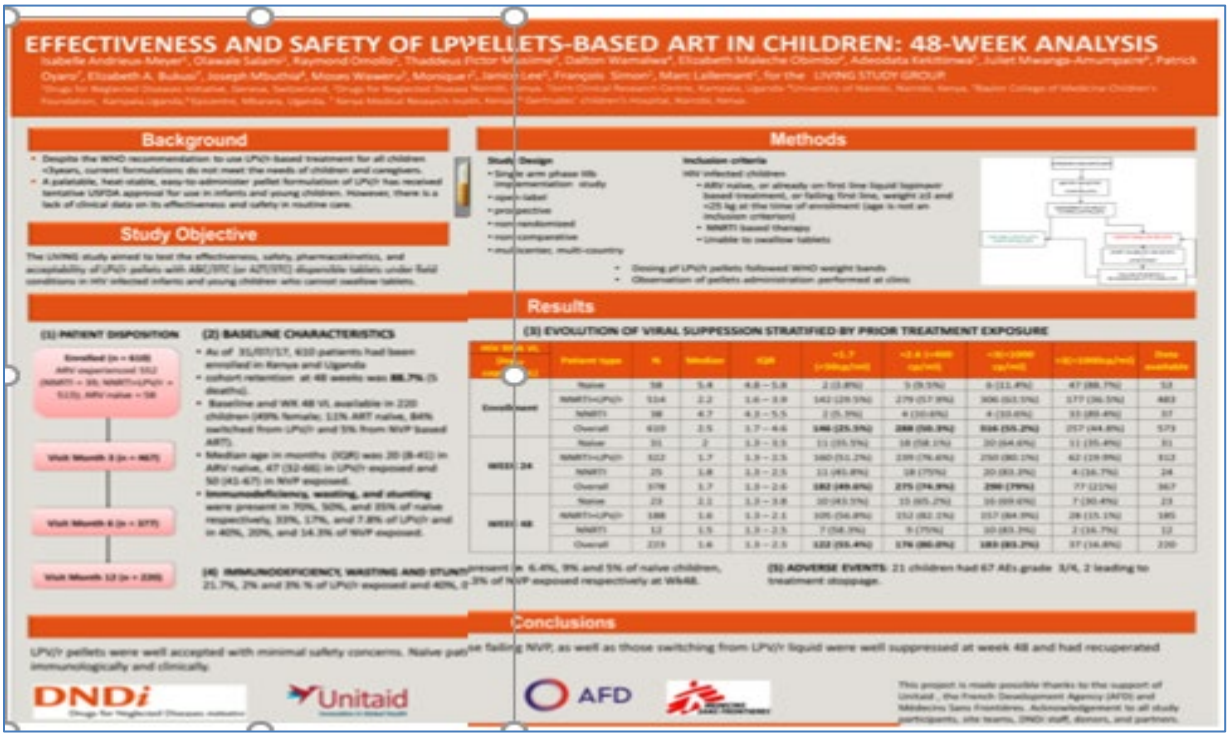
- The acceptance of the new LPV/r pellet formulation is high and ultimately may contribute to long-term adherence.
- Since food shortages were observed in some households, providing the medication with liquids (tea, water) was helpful in maintaining adherence.
- Supportive caregiver-health care provider communication is essential to convey correct instructions for administering the LPV/r pellets, while attention for contextual barriers is needed (HIV-related stigma, poverty-related challenges).
- The LIVING trial builds on positive organizational factors such as adherence support counseling, which is appreciated by the caregivers, and which contributed to an increased number of mother-child dyads being able to maintain adherence. The influence of structural-contextual factors need to be considered.

This project is made possible thanks to Unitaid's support. Acknowledgement to all the caregivers and clinical trial staff who participated in the study.

DNDi Unitaid INSTITUTE OF TROPICAL MEDICINE AFD MEDECINS SANS FRONTIERES

19th ICASA CONFERENCE 4-9th DECEMBER IVORY COAST

• ***KEMRI Annual Scientific and Health (KASH) Conference – Feb. 15, 2018 (Nairobi) – General presentation*** made on DNDi to celebrate its 15th anniversary with section on achievements in Paediatric HIV • Conference on Retroviruses and Opportunistic Infections (CROI) – Mar. 4-7, 2018 (Boston) – Poster presentation: "Effectiveness and Safety of LPV/r Pellets-based ART in Children: 48-Week Analysis" (see below).



• ***Conférence Internationale Francophone VIH/Hépatites (AFRAVIH) – Apr. 4-7, 2018*** (Bordeaux) – A presentation was made during the Unitaid-supported symposium about optimal child-adapted antiretroviral formulations. DND*i*'s work in Paediatric HIV was also shared at Unitaid's booth.

• ***MSF Scientific Days – May 24-25, 2018 (London) – A poster presentation: "Virological Outcomes, Safety and Acceptability of LPV/r Pellets-Based ART in Young Children: 48-Week Interim Analysis of the LIVING Study".*** This poster received the best poster award at this meeting (see below).

Virological Outcomes, Safety and Acceptability of LPV/r Pellets-Based ART in Young Children: 48-Week Interim Analysis of the LIVING Study.

Andrieux-Meyer I[1], Salami O[2], Wamalwa D[3], Musiime V[4], Oyaro P[5], Musoke R[6], Mbuthia J[7], Nyandiko W[8], Omollo R[2], Obimbo E[9], Bukusi E[5], Mwanga-Amumpaire J[9], Egondi T[2], Simon F[1], Odhiambo S[2], Kyomuhendo F[2], Waweru M[2], Lee J[1], Kekitiinwa A[10], Lallemant M[1]

[1]Drugs for Neglected diseases initiative, Geneva, Switzerland, [2]Drugs for Neglected diseases initiative, Nairobi, Kenya, [3]University of Nairobi, Nairobi, Kenya, [4]Makerere University, Kampala, Uganda, [5]Kenya Medical research institute, Nairobi, Kenya, 6CDGRI/Lea -Toto, Nairobi, Kenya, [7]Gertrude's Children's Hospital, Nairobi, Kenya, [8]AMPATH/ Moi University, Eldoret, Kenya, [9]Epicentre, Mbarara, Uganda, [10]Baylor university centre of excellence in pediatric HIV, Kampala, Uganda

Background

- There are limited options for first line ARVs in infants and young children.
- The current tablet and syrup formulations of LPV/r are not suitable for use for very young children and their caregivers.
- DNDi has worked with CIPLA to develop a new pellet formulation of LPV/r which is palatable, heat-stable, taste-masked and easy-to-administer.

- The pellets formulation has been approved for use in infants and young children. However, there is limited clinical data on its effectiveness and safety in routine care.

Study Objectives

The LIVING study aims to evaluate the effectiveness, safety, PK and acceptability of LPV/r pellets + standard NRTIs in HIV+ children unable to swallow tablets.

Methods

Inclusion criteria

- HIV infected children
- ARV naïve, or already on first line liquid lopinavir-based treatment, or failing first line, NNRTI based therapy
- weight ≥3 and <25 kg at the time of enrolment (age is not an inclusion criterion)
- Unable to swallow tablets

Exclusion criteria

- Treatment failure with the presence or strong suspicion of a PI resistance mutation
- Current treatment with a drug that interacts significantly with LPV/r
- Clinically significant disease in the investigator's opinion, which would compromise participation in the study
- Treatment with experimental drugs for any indication within 30 days prior to study entry
- Anticipated transfer to non study treatment site.

Study Design

- Single-arm phase IIIb implementation study
- open-label
- prospective
- non-randomized
- non-comparative
- multicentre, multi-country

- Dosing of LPV/r pellets followed WHO weight bands
- Observation of pellets administration performed at clinic
- Enrolment completed across 12 sites in Kenya, Uganda and Tanzania

Results

1. Patient disposition

Enrolled (n=715)
ARV experienced = 641
NNRTI = 42
NNRTI+LPV/r = 599
ARV naïve = 74

Visit M-6 (n = 459)

Visit M-12 (n = 305)

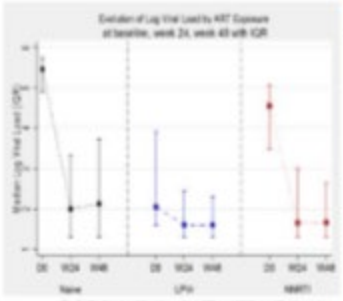
Complete VL results available for n=266, data as of 31/10/2017

	n	%
Sex		
Male	130	48.9
Female	136	51.1
Treatment exposure		
ART naïve	25	9.4
Lopinavir	229	86.1
NNRTI	12	4.5

2. Baseline characteristics

	ART naïve		NNRTI+LPV/r		NNRTI		Total	
	median	95% CI	median	95% CI	median	95% CI	median	95% CI
ART duration (weeks)	0.0	0.0 0.0	26.8	10.6 45.8	32.6	14.2 39.5	27.1	11.4 45.7
Age (weeks)	20.0	11.0 38.0	44.0	28.0 63.0	52.5	43.5 62.5	43.0	25.0 62.0
Weight (kg)	9.0	6.2 11.7	14.0	11.0 16.0	14.8	11.6 16.8	13.8	10.7 16.0
VL log10 copies/ml	5.5	4.9 5.7	2.0	1.6 3.8	4.6	3.5 5.1	2.4	1.6 4.6

3. Virological outcome



		n	Median Log 10 cp/ml	IQR		<50 copies	≥400 cp/ml	≥1000 cp/ml	≥1000 cp/ml
Baseline	ART naïve	25	5.5	4.9	5.7	1(4.0%)	1(4.0%)	1(4.0%)	24(96.0%)
	NNRTI+Lopinavir	229	2.0	1.6	3.9	77(33.6%)	138 (60.3%)	153 (66.8%)	76(33.2%)
	NNRTI	12	4.6	3.5	5.1	1(8.3%)	2 (16.7%)	2(16.7%)	10(83.3%)
	Overall	**266**	**2.4**	**1.6**	**4.7**	**79(29.7%)**	**141(53.0%)**	**156(58.7%)**	**110(41.4%)**
Month 6	ART naïve	25	2.0	1.3	3.3	9(36.0%)	15(60.0%)	16(64.0%)	9(36.0%)
	NNRTI+Lopinavir	229	1.6	1.3	2.4	121(52.8%)	177(77.3%)	186(81.2%)	43(18.8%)
	NNRTI	12	1.7	1.3	3.0	6(50.0%)	8(66.7%)	9(75.0%)	3(25.0%)
	Overall	**266**	**1.7**	**1.3**	**2.6**	**136(51.1%)**	**200(75.2%)**	**211(79.3%)**	**55(20.7%)**
Month 12	ART naïve	25	2.1	1.3	3.7	12(48.0%)	16(64.0%)	17(68.0%)	8(32.0%)
	NNRTI+Lopinavir	229	1.6	1.3	2.3	127(55.5%)	182(79.5%)	187(81.7%)	42(18.3%)
	NNRTI	12	1.7	1.3	2.6	6(50.0%)	9(75.0%)	10(83.3%)	2(16.7%)
	Overall	**266**	**1.6**	**1.3**	**2.5**	**145(54.5%)**	**207(77.8%)**	**214(80.5)**	**52(19.6%)**

4. Ease of administration of pellets

Response from caregiver	Month 3, n=548*	Month 6, n=454*	Month 12, n=297*
Very easy, n (%)	246 (44.9%)	216 (47.6%)	154 (51.9%)
Easy, n (%)	194 (35.4%)	149 (32.8%)	94 (31.6%)
Average, n (%)	63 (11.5%)	48 (10.6%)	29 (9.8%)
Difficult, n (%)	21 (3.8%)	24 (5.3%)	11 (3.7%)
Most difficult, n (%)	5 (0.9%)	4 (0.9%)	0%
Pending, n (%)	19 (3.5%)	13 (2.9%)	9 (3%)

5. Adverse events

- 36 children had 74 grade 3/4 AEs.
- 2 AEs led to treatment discontinuation.

Conclusion

Naïve children failing NVP, as well as those switching from LPV/r syrup were well suppressed at week 48. LPV/r pellets were well accepted with minimal safety concerns.

Acknowledgements

This project has been made possible thanks to the support of Unitaid, the French Development Agency (AFD), and Médecins Sans Frontières. We also acknowledge here all study participants, site teams, DNDi staff, and partners.

• ***Tanzanian Paediatric HIV conference – Jun. 6-7, 2018 (Tanzania)*** – Presentation was made on the outcomes of the use of 2-in-1 pellets in children, which was well received. Attendees included paediatric HIV stakeholders in Tanzania: paediatricians, the Ministry of Health (MoH), Clinton Health Access Initiative, UNAIDS, Unicef and Elizabeth Glaser Pediatric AIDS Foundation.

• ***International AIDS Society (IAS) Conference – Jul. 21-24,*** 2018 (Amsterdam) – DNDi participated in a satellite session (organized in collaboration with the African Society for Laboratory Medicine, EGPAF, CHAI, UNICEF and Unitaid) that shared experience on diagnosis and treatment and what's being currently done in the field. DNDi provided early data on the LPV/r pellets as part of the LIVING Study.

• ***ART Optimization Programme Advisory Committee Meeting – Sep. 24-25, 2018 (Geneva) – Presentation on DNDi Paediatric HIV program made, including sharing of updates on LIVING and LOLIPOP Studies***

• ***Southern African HIV Clinicians Society Conference (SAHCS) – Oct. 24-27, 2018 (Johannesburg) –*** **DND*i's Head of the South Africa Office, Carol Ruffell made a presentation on field learnings of optimizing paediatric HIV formulations***.

• ***High-Level Dialogue to Assess Progress on and Intensify Commitment to Scaling Up Diagnosis and Treatment of Paediatric HIV" meeting – Dec. 6-7, 2018*** (Vatican City) – DNDi committed to continue collaborating with all relevant stakeholders on accelerating product uptake for solid oral dosage forms of LPV/r (2-in-1 and 4-in-1).