Making medical history

TO MEET THE NEEDS OF NEGLECTED PATIENTS

2018 - 2019
DND*i* R&D PROGRAMMES IN FOCUS

DND*i*
Drugs for Neglected Diseases *initiative*

Contents

2018 - 2019 R&D DND*i* Programmes in Focus

The **Drugs for Neglected Diseases *initiative* (DND*i*) was created to address the 'fatal imbalance' – the major unmet treatment needs of the world's poorest people**, who have been failed by market-driven R&D for medicines, diagnostics, and other health commodities. DND*i* works through collaborations with world-class research institutions and pharmaceutical companies in all phases of drug discovery research and development.

By mid-2019, DND*i* had 45 R&D projects in portfolios for seven viral and neglected tropical diseases, including 20 new chemical entities and more than 20 ongoing clinical trials.

This R&D Programmes in Focus provides information on all DND*i*'s current projects, from drug discovery through registration and implementation. **2018 was a milestone year** for DND*i* and for our many partners. We celebrated the **15th anniversary since our founding** with the delivery of **DND*i*'s first new chemical entity, fexinidazole**, a completely new drug and the first-ever oral treatment for sleeping sickness, developed with partners from 'bench to bedside'.

Another 2018 success came when the **Global Antibiotic Research & Development Partnership (GARDP) became a separate legal entity** after a successful three-year incubation by DND*i*. GARDP was created in 2016 by the World Health Organization and DND*i* to develop new or improved antibiotic treatments in a context of growing antimicrobial resistance. During its hosting by DND*i*, GARDP built a skilled and dedicated team, formed a Board of Directors, forged partnerships with industry and academia, and launched clinical programmes to develop antibiotics for drug-resistant infections for children, newborns with sepsis, and sexually-transmitted infections.

Among **other highlights from 2018**:

- interim results of clinical trials in Malaysia and Thailand assessing an affordable hepatitis C combination treatment that includes the new drug ravidasvir showed the combination to be safe and effective, with very high cure rates, even in hard-to-treat cases.
- interim results of the 'LIVING' study of more than 1,000 children living with HIV in Kenya and Uganda showed that pellets containing two antiretroviral drugs were well-tolerated and improved clinical outcomes in very young children.
- a study in Bangladesh confirmed that post-kala-azar dermal leishmaniasis can be a reservoir for the transmission of visceral leishmaniasis (VL) – important evidence for VL elimination efforts in South Asia.
- a study in Ethiopia found that a treatment combination, and sometimes a second course of drugs, is most effective to treat VL in people co-infected with HIV.
- two Phase I studies in healthy volunteers for potentially macrofilaricidal drugs were successful and will advance to Phase II.
- a Phase II trial in Bolivia, BENDITA, which evaluated varying treatment durations and dosages of benznidazole for Chagas, found that shorter treatment could be just as effective and significantly safer.
- patient enrolment was completed for a Phase III trial of acoziborole, a new, oral, single-dose sleeping sickness treatment, with results expected in 2020 after last patient follow-up.
- a new collaboration began with GlaxoSmithKline and the University of Dundee Drug Discovery Unit to identify drug candidates for leishmaniasis and Chagas disease.
- 45 patients were enrolled for a Phase II proof-of-concept study in Spain to test different short-course regimens of fexinidazole for adults with chronic indeterminate Chagas, to be completed in late 2019.

2018 - 2019 R&D HIGHLIGHTS

AN END-TO-END APPROACH, FROM DRUG DISCOVERY TO IMPLEMENTATION

DISCOVERY

DNDi works with partners to screen millions of chemical compounds. Promising compounds are evaluated and optimized to produce just one or two drug candidates with potential.

TRANSLATION

DNDi and partners assess drug candidates for safety and develop compounds into medicines that can be given to patients. Drugs are first tested in a small number of healthy volunteers, followed by studies with a small number of patients to establish therapeutic dosing levels.

NEW COLLABORATION TO IDENTIFY DRUG CANDIDATES

In March, DND*i* began a collaboration with GlaxoSmithKline and the University of Dundee Drug Discovery Unit to discover new pre-clinical drug candidates targeting leishmaniasis and Chagas disease.

OPEN-SOURCE, VIRTUAL DRUG DISCOVERY PROJECTS GAIN MOMENTUM

The Mycetoma Open Source (MycetOS) project was launched by the University of Sydney, Erasmus MC, and DND*i*, using an open source approach to discover potential treatments for mycetoma. DND*i*'s Open Synthesis Network, which engages medicinal chemistry students in research for neglected diseases, expanded to more than 20 participating institutions by year end.

EIGHTH COMPANY JOINS DND*i* NTD DRUG BOOSTER

The NTD Drug Discovery Booster enables more efficient screening of potential drug compounds, while benefiting from access to pharmaceutical partners' compound libraries. In 2018, Astellas (Japan) joined the Booster, which, by the end of the year, had produced six series that have progressed to proof-of-concept studies for leishmaniasis and Chagas disease.

POTENTIAL NEW DRUGS FOR VISCERAL LEISHMANIASIS PROGRESS TO PHASE I

In a bid to radically transform patient therapy, from today's complex and toxic treatments to patient-friendly, simple oral therapies, DND*i* has built an unprecedented portfolio of oral drug candidates with donors and partners from industry and academia. Two of these – DNDI-0690 and DNDI-6148 – are now progressing to Phase I studies, to start in 2019.

EMODEPSIDE AND TYLAMAC COMPLETE PHASE I TESTING

Two Phase I studies in healthy volunteers for potentially macrofilaricidal drugs were successfully completed for emodepside (Bayer) and the antibiotic TylAMac (AbbVie). Phase II studies are planned.

POTENTIAL CHAGAS DRUG CANDIDATE MAY EMERGE FROM DAIICHI SANKYO PROJECT

A project milestone was reached with the proven efficacy of a new compound against Chagas disease, which the partners hope to progress to the next stage of pre-clinical research in 2019.

CLINICAL DEVELOPMENT

With partners, DNDi conducts large-scale clinical trials with people affected by the disease, to confirm the new drug's safety and efficacy.

IMPLEMENTATION & TREATMENT ACCESS

DNDi supports dossier preparation for drug regulatory review and national registration, collects additional data on the use of new drugs in every-day clinical contexts, and works with health ministries and affected communities to tackle barriers to accessing treatment.

HEPATITIS C DRUG COMBINATION SHOWS 97% CURE RATE

Interim results of a DND*i* clinical trial showed the treatment combination of new drug candidate ravidasvir with sofosbuvir to be safe and effective, with very high cure rates for patients, including hard-to-treat cases.

BETTER VL TREATMENT COMBINATION FOR EAST AFRICA?

Based on good results with combination therapies to treat visceral leishmaniasis (VL) in South Asia, a Phase III study started in April in Ethiopia, Kenya, Sudan, and Uganda to compare combination regimens of miltefosine and paromomycin with current treatment, which has side effects.

PUTTING THE SPOTLIGHT ON PKDL

Results of a DND*i* study in Bangladesh confirmed that post-kala-azar dermal leishmaniasis (PKDL) is a reservoir for transmission of VL and could thus threaten elimination efforts in South Asia. The findings highlight the importance of prompt diagnosis and treatment and the need for better drugs. A new PKDL treatment study began in Sudan in September.

WORLD'S FIRST MYCETOMA CLINICAL TRIAL REACHES INTERIM ANALYSIS

The first-ever clinical trial for fungal mycetoma, underway in Sudan, enrolled 84 patients by year end, the recruitment threshold for interim analysis. The study is evaluating the efficacy of anti-fungal fosravuconazole with hopes for a more effective and affordable treatment for this most neglected of diseases.

BETTER TREATMENT FOR HIV/VL CO-INFECTION

Results from a DND*i* study in Ethiopia showed greater success with a treatment combination for people living with HIV who are co-infected with VL. These findings should pave the way for guideline change at national and international levels.

SHORTER CHAGAS TREATMENT COULD BE JUST AS EFFECTIVE

A two-week treatment course of benznidazole for adult patients with chronic Chagas disease showed similar efficacy and significantly fewer side effects than the standard eight-week treatment, according to a DND*i* clinical trial in Bolivia.

ENROLLMENT COMPLETED FOR SINGLE-DOSE SLEEPING SICKNESS TREATMENT

Following expansion of the acoziborole study to three new sites in two countries, DND*i* successfully reached the target number of patients, with results expected in 2020.

FEXINIDAZOLE - PARADIGM SHIFT FOR SLEEPING SICKNESS TREATMENT

In November, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a 'positive scientific opinion' of the first oral treatment for both stages of sleeping sickness, the result of a ten-year partnership between DND*i*, Sanofi, and health ministry partners. Just 39 days later, the drug was registered in the Democratic Republic of Congo, where 70% of cases are found.

'2-IN-1' FORMULATION FOR CHILDREN LIVING WITH HIV PROVES EFFECTIVE

In February, interim results of DND*i*'s implementation study showed that easy-to-take, heat-stable '2-in-1' pellets were well-tolerated and improved clinical outcomes in children living with HIV. DND*i* continues to work on development of '4-in-1' granules to be sprinkled on food or in milk, simpler and safer treatment for children too young to swallow pills.

EXPANDING ACCESS TO CHAGAS DIAGNOSIS & TREATMENT

DND*i* and the Colombian Ministry of Health and Social Protection are piloting a simpler model of care to increase access to Chagas diagnosis and treatment, and a similar project is starting in Brazil with the Oswaldo Cruz Foundation and national stakeholder groups. In addition, funds from the sale of the priority review voucher awarded to Chemo Research for FDA registration of benznidazole will be devoted to improving patient access to diagnosis and treatment as outlined in the Global Access Framework for Chagas Disease by DND*i* and the Fundación Mundo Sano.

SUPPORTING MALAYSIAN EFFORTS FOR HEPATITIS C SCREENING AND TREATMENT

FIND and DND*i* teamed up in July to generate evidence to support policy change and scale-up of hepatitis C diagnosis and treatment throughout the Malaysian public health system. The project is decentralizing screening with rapid diagnostic tests and linking people to treatment, including in a DND*i* clinical trial.


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HUMAN AFRICAN TRYPANOSOMIASIS
(HAT, OR SLEEPING SICKNESS)

DND*i* aims to deliver new oral treatments to cure sleeping sickness that are safe, affordable, effective and easy to use, and support the sustainable elimination of the disease.

DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
		SCYX-13330682 ⊕ SCYX-1608210				Acoziborole ⊕		Fexinidazole for *T.b. gambiense* ⊕
						Fexinidazole for *T.b. rhodesiense*		Nifurtimox-eflornithine combination therapy (NECT)

⊕ New chemical entity

June 2019

SCYX-1330682 & SCYX-1608210

Objective: Maintain back-up drug candidate oxaboroles to replace the drug candidate acoziborole, if needed

DND*i* continues to provide support and advice to researchers working on discovery of new candidates for HAT and maintains two back-up candidates from the oxaborole class to ensure future development options, if needed.

Acoziborole

Objective: Develop and register acoziborole as a new, single-dose, oral treatment

The delivery of fexinidazole *(see right)* has improved therapeutic options for people with sleeping sickness. But the development of an additional, oral treatment, especially one that could be given as a one-day, one-dose treatment, could provide even better options, as well as supporting efforts to eliminate and sustain elimination of the disease.

In 2012, acoziborole became DND*i*'s first new chemical entity, resulting from DND*i*'s own lead optimization programme, to enter clinical development. Phase I trials were completed in 2015 and allowed the therapeutic dose to be determined, administered as a single dose of three tablets. A pivotal Phase II/III trial started in 2016 to study the safety and efficacy of this new chemical entity potential as a treatment for stage-2 HAT caused by *T.b. gambiense* (g-HAT) that could also be safe and effective for stage 1 of the disease.

In 2018, recruitment of patients continued with 189 patients enrolled by the end of the year, including 155 patients with late stage-2 disease, and the target enrolment of 210 patients reached by March 2019. Four new clinical sites in the Democratic Republic of Congo (DRC) were added to the already active sites and a new site was opened in Guinea.

Delivered

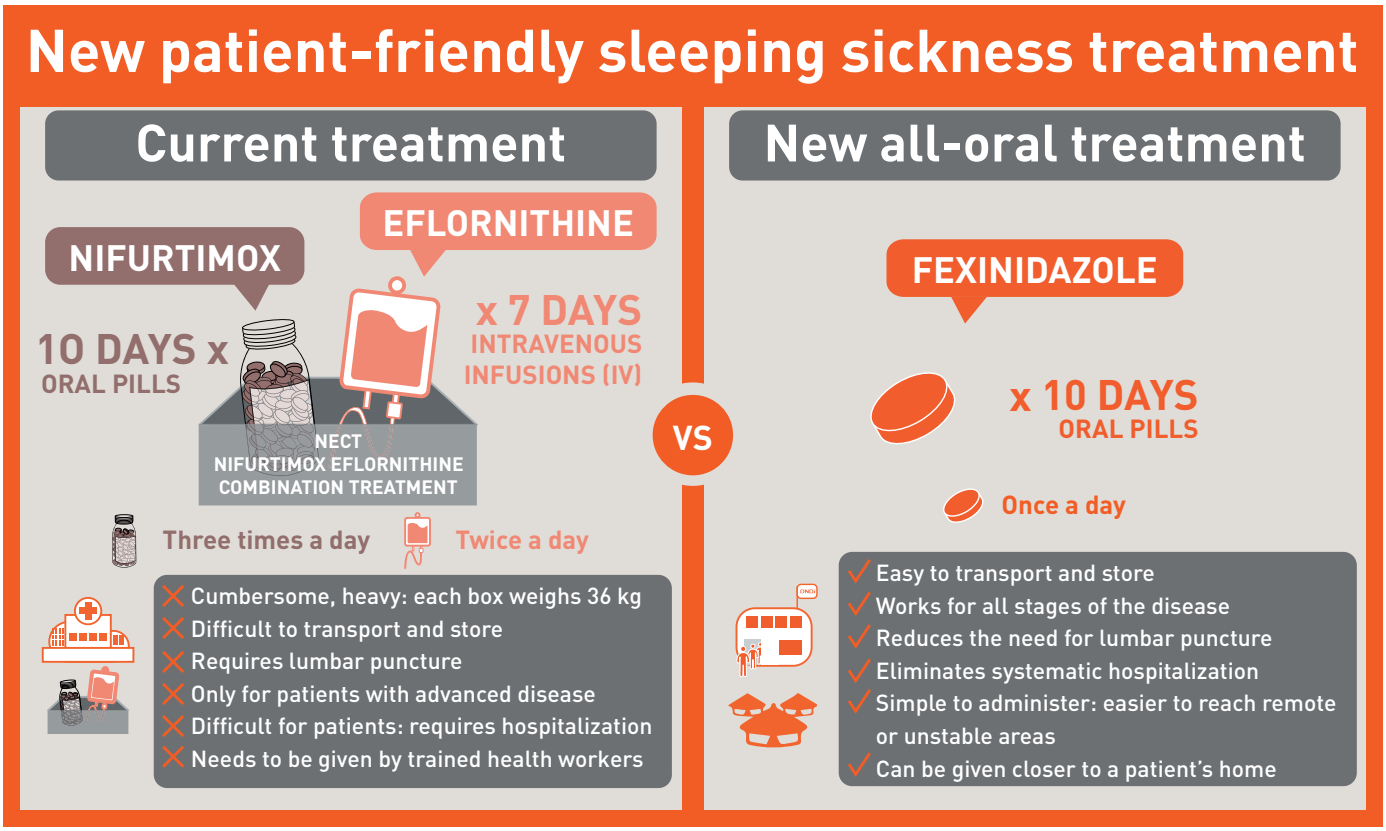
Fexinidazole

In 2005, DND*i* undertook an extensive compound mining exercise and identified fexinidazole, whose pre-clinical development had been shelved by Hoechst AG (now Sanofi) in the 1980s. After completing pre-clinical studies, DND*i* partnered with Sanofi in 2009 for the development, manufacturing, and distribution of fexinidazole. Phase I studies started in 2010, and a Phase II/III clinical trial began in the DRC and the Central African Republic (CAR) in 2012.

Fexinidazole received a positive scientific opinion by the European Medicines Agency's Committee for Medicinal Products for Human Use in November 2018 and was registered in the DRC in December 2018. It is the first new chemical entity to be developed by DND*i*.

Fexinidazole will be donated by Sanofi to the World Health Organization (WHO) for distribution to national sleeping sickness control programmes in endemic countries, and patients should have access to the drug in the coming months.

DND*i* will continue to support implementation of and access to fexinidazole as a new all-oral treatment for the treatment of stage-1 and stage-2 HAT caused by *T.b. gambiense* (g-HAT) in adults and children.



Ongoing fexinidazole studies

DND*i*'s investment in fexinidazole is not yet over.

In 2016, DND*i* initiated a Phase IIIb trial to obtain more clinical data on specific populations not included in previous trials, including pregnant and breast-feeding women, and people with poor nutritional status or chronic diseases. Patients are treated either in hospital or at home, thereby also providing preliminary information about treatment adherence and final effectiveness in ambulatory patients. In 2018, two new clinical sites in the DRC and one in Guinea were added and 116 patients enrolled.

In addition, a Phase IV study to support access to fexinidazole and collect pharmacovigilance data is also under preparation. The first patients are expected to be enrolled by the end of 2019.

Lastly, a Phase II/III study is being prepared in Malawi and Uganda to assess fexinidazole to treat sleeping sickness caused *by T.b rhodesiense*, the other, more virulent subspecies of the parasite affecting humans, occurring primarily in Eastern Africa. The study will start in mid-2019.

Delivered

Nifurtimox-eflornithine combination therapy (NECT)

Before 2009, treatment for sleeping sickness based on eflornithine alone was extremely complex to distribute and administer. All too often, doctors would have no choice but to use melarsoprol, a highly toxic, arsenic-based drug that killed one in 20 patients.

In 2009, results from DND*i*/MSF-sponsored clinical trials showed that NECT, a combined treatment of Bayer's nifurtimox and Sanofi's eflornithine, was safe and effective to cure sleeping sickness. NECT has significant practical benefits: treatment is simpler, shorter, and more cost effective than using eflornithine alone. NECT was included on the WHO Essential Medicines List in 2009 and the Essential Medicines List for Children in 2013.

Today, while we await new WHO treatment guidelines for sleeping sickness following the positive scientific opinion of fexinidazole by the EMA, under its Article 58 procedure, and subsequent approval for use in DRC, NECT is recommended as the first-line treatment in all endemic countries, all of which receive free supplies through WHO via drug donations.

LEISHMANIASIS

DND*i* aims to make treatments safer, shorter, and more affordable and effective for all forms of leishmaniasis. In the short term, better treatment regiments are being developed using existing drugs. In the long term, the goal is to develop an entirely new generation of all-oral drugs.

DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
Screening	Leishmaniasis Hit-to-lead	DNDI-5421 ⊕ DNDI-5610	DNDI-5561 ⊕	DNDI-6148 ⊕		New CL combination	New VL treatments (Latin America)	SSG&PM (East Africa)
	NTD Drug Discovery Booster Hit-to-lead	Amino-pyrazoles ⊕	GSK3494245 ⊕ DDD1305143	DNDI-0690 ⊕		New treatments for PKDL	New treatments for HIV/VL	New VL treatments (South Asia)
	Daiichi Sankyo Hit-to-lead	CF series ⊕	CpG-D35 for CL ⊕	GSK3186899 ⊕ DDD853651		Miltefosine + paromomycin combination (Africa)		
		Leishmaniasis L205 Series ⊕						

⊕ New chemical entity

June 2019

Screening

Objective: Deliver a robust portfolio of drug discovery hit and lead series for leishmaniasis

DND*i* is searching for chemical compounds with activity against *Leishmania* parasites. High-throughput screening of diverse compound libraries from pharmaceutical companies, biotechs, and commercial vendors have been completed against *Leishmania donovani*, in collaboration with screening partners University of Dundee and Institut Pasteur Korea.

Several new starting points from screening are now currently being followed up in hit profiling, annotation, and subsequent hit-to-lead programmes. The screening effort will continue, with the aim of delivering further drug candidates to mitigate the risks of attrition and increase the chance of developing a new drug.

Hit-to-lead

Objective: through collaborative hit-to-lead projects, identify new leads with activity in animal models of disease and the potential for further optimization

The aim of hit-to-lead projects is to convert the hits from *in vitro* screening into leads with activity in animal models of disease and the potential for further optimization.

Projects include:

- Through the **NTD Drug Discovery Booster** project, DND*i* brings together pharmaceutical companies in a non-competitive search to speed up the process and cut the cost of finding new treatments for leishmaniasis. The project conducts multilateral, simultaneous searches of millions of compounds based on an active seed supplied by DND*i* and uses computational approaches to refine the search iteratively. In 2018, the Japanese pharmaceutical company Astellas Pharma Inc. became the eighth company to join the consortium (after AbbVie, AstraZeneca, Celgene, Eisai, Merck, Shionogi, and Takeda). Since its creation in 2015, the Booster has launched 45 iterations around 22 seed compounds, with the result that 13 hit series have been released, of which six have progressed to *in vivo* proof-of-concept studies for Chagas disease and/or leishmaniasis.
- **DND*i* partnered with Japanese pharmaceutical company Daiichi Sankyo** in a hit-to-lead project that ended in September 2018.

Novel consortium formed to find and develop new therapy for leishmaniasis

DND*i*'s long-term goal in leishmaniasis is to radically transform patient therapy: from today's complex, poorly-adapted and -tolerated treatments, to patient-friendly, simple oral therapies that are short-course, affordable, safe, and efficacious in both children and adults.

Together with partners at the Drug Discovery Unit and Wellcome Trust Centre for Anti-Infectives Research at the University of Dundee (DDU), pharmaceutical companies GlaxoSmithKline (GSK), Pfizer, Takeda, and Celgene, and the product development partnership TB Alliance, with the support of the GHIT Fund, DND*i* has built an unprecedented portfolio of lead series, pre-clinical, and clinical candidates for leishmaniasis from different chemical classes with different mechanisms of action against *Leishmania* parasites.

In a novel consortium with these partners, DND*i* will work to advance this unique portfolio, with the goal of progressing drug candidates through Phase I clinical development, and for the most promising clinical candidates to be selected for a Phase II clinical trial testing the safety and efficacy of a combination of two entirely new chemical entities.

The consortium provides a strong basis for advancing towards oral leishmaniasis therapies, in priority for VL and potentially also for CL, and it provides options to overcome attrition in drug development. It brings together several projects at various stages:

Lead optimization projects:

- **Celgene Global Health visceral leishmaniasis series 1:** Because of poor pharmacokinetics and a lack of safety margins following extensive exploration, the decision was made to stop this series. A new screen has begun with a new sub-set of the Celgene library of compounds with the goal to identify novel lead series with better drug-like properties.
- **Leishmaniasis L205 series:** Lead compound DNDI-6588 showed great efficacy in vivo in both mouse and hamster models for VL. Additional 205-series compounds with similar or improved profiles have been added to the candidate shortlist and are currently being assessed.
- **Aminopyrazoles:** Further work on the back-ups from this series is currently on hold as efforts focus on the lead compound DNDI-5561. However, new chemical spaces continue to be investigated through the Open Synthesis Network, a collaborative project that engages master's and undergraduate students in research for neglected diseases.
- **DNDI-5421 and DNDI-5610:** Further work on the back-ups from the oxaborole series is currently on hold as efforts focus on the lead compound DNDI-6148.

Compounds in clinical Phase I studies or close to entering Phase I:

- **DNDI-0690:** Nitroimidazole derivatives hold great potential to address unmet needs in tuberculosis (TB) therapy. As well as developing a clinical candidate for TB, the TB Alliance instituted a backup programme to maximize the potential of this class of anti-bacterial agents. Through a contractual agreement with TB Alliance, DND*i* gained access to a library of around 70 nitroimidazoles which were then tested for potential anti-leishmanial activity. DNDI-0690 was nominated as a pre-clinical candidate in 2015, and in 2018 the decision was made to progress to a first-in-human Phase I single ascending dose in healthy volunteers in 2019.

- **DNDI-6148:** DND*i*'s screening of Anacor's library of drug compounds from the oxaborole class, followed by focused medicinal chemistry efforts, led to the discovery of a number of analogues showing efficacy in animal models of sleeping sickness, Chagas, and leishmaniasis. While one of these compounds, acoziborole, is currently progressing in Phase II/ IIII trials for sleeping sickness, an analogue, DNDI-6148 was shown in various *in vitro* and *in vivo* studies to be effective against *Leishmania* strains. The decision was made in 2018 to progress to a first-in-human Phase I single ascending dose in healthy volunteers. The clinical trial application for this study will be submitted in 2019.
- **DNDI-5561:** DNDI-5561 is the most advanced compound of the aminopyrazole series. DND*i* developed the series from a single high-throughput screening hit, which was originally identified in an *in vitro* screen of Pfizer's compound library. A hit-to-lead project conducted by DND*i* produced improved leads with activity in animal models of leishmaniasis. The optimization of these leads to produce DNDI-5561 was achieved in a partnership between DND*i*, Takeda, and the GHIT Fund. Pre-clinical studies to enable a first-in-human study (Phase I) started in February 2018 and should be completed by the end of 2019.
- **GSK3186899/DDD853651 and GSK3494245/DDD1305143:** In 2017, DND*i* and GSK entered into an agreement for the pre-clinical development of two compounds for leishmaniasis developed by a collaboration between the Global Health unit within GSK and the Drug Discovery Unit at the University of Dundee, supported by co-funding by Wellcome. GSK3186899/DDD853651 was nominated as a clinical candidate in 2018. GSK3494245/DDD1305143 is under review to assess the feasibility of proceeding to a Phase I study.

CpG-D35 for cutaneous leishmaniasis (CL)

Objective: Demonstrate the suitability of an immunomodulator to stimulate the innate immune system to fight the parasitic infection responsible for CL

This project aims to produce, in partnership with GeneDesign, an immunomodulator to stimulate the innate immune system to fight *Leishmania* infection, as an adjunct to drug therapy.

Final results of the preclinical *in vivo* efficacy study showed an improved outcome for CpG-D35, either alone or in combination with pentavalent antimony (glucantime). The pre-clinical package to enable a first-in-human study (Phase I) will be performed in 2019. A meeting is planned for 2019 with the UK Medicines and Healthcare Products Regulatory Agency to discuss the pre-clinical development plan and clinical package.

New cutaneous leishmaniasis combination therapies

Objective: Explore whether existing approved treatment approaches for CL are more effective when used in combination

In uncomplicated CL cases (people with a small number of lesions, not located on the face or on joints), thermotherapy – applying heat to the wound for a short duration – is the most practical treatment option.

This Phase II study aims to assess whether a combination of thermotherapy with a shorter course of oral miltefosine achieves better results than thermotherapy alone.

Patient enrolment was completed in Peru and Colombia (65 patients in each country) in August 2018, and the last patient was expected to be given a six-month follow-up in February 2019.

Interim results support the preparation of a Phase III study which is being planned in five sites across four countries in Latin America, in which the combination will be compared against the standard treatment for CL in the Americas – meglumine antimoniate – which comes with risks of potential toxicity.

New treatments for HIV/VL

Objective: Identify and deliver a safe and highly effective treatment for VL in HIV co-infected patients that will improve their long-term survival

People co-infected with HIV and VL rarely achieve sustainable control of the parasite and present multiple episodes of relapse. In 2011, MSF began using a compassionate regimen, combining liposomal amphotericin B (often better known as AmBisome, the brand name of the drug produced by Gilead) with the oral drug miltefosine in Abdurafi Health Centre in North-West Ethiopia. To provide the necessary scientific evidence, DND*i* ran a Phase III study, starting in 2014, testing both AmBisome monotherapy as per current WHO and international recommendations, and a combination of AmBisome infusion and miltefosine orally for 28 days in 58 HIV/VL patients in two sites in Ethiopia.

Results demonstrated the high efficacy of the combination therapy with a 67% cure rate when treatment lasted 28 days, increasing to an 88% cure rate when patients who were not cured received a second round of treatment to clear the parasite, with a full treatment lasting 58 days. Results were presented to the authorities in Ethiopia, and guidelines are under review to consider adopting the new combination treatment.

In addition, top-line results of a Phase III study sponsored by MSF in India, in which DND*i* and the Rajendra Memorial Research Institute acted as technical partners, are expected in 2019. These complementary results should support discussions with national and international stakeholders for a new treatment recommendation for VL in people co-infected with HIV.

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

A randomized trial of AmBisome monotherapy and AmBisome and miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients in Ethiopia

Diro E, Blesson S, Edwards T, Ritmeijer K, Fikre H, Admassu H, Kibret A, Ellis S, Bardonneau C, Zijlstra EE, Soipei P, Mutinda B, Omollo R, Kimutai R, Omwalo G, Wasunna M, Tadesse F, Alves F, Strub-Wourgaft N, Hailu A, Alexander N, Alvar J.

January 2019

Treatments for post-kala-azar dermal leishmaniasis (PKDL)

Objective: Determine the safety and efficacy of treatment regimens for people with PKDL in East Africa and South Asia, and understand the role of PKDL in VL transmission

PKDL is a non-lethal complication of VL which can develop months or years after VL treatment has been completed, and can be severely disfiguring and stigmatizing, as the symptoms are characterized by a skin rash, often on the face. Better treatment options are needed, as existing treatments include options that are expensive and lengthy, with complex administration and potentially toxic effects.

In Sudan, a Phase II study to test both liposomal amphotericin B in combination with miltefosine, and paromomycin in combination with miltefosine began in Dooka, Sudan in 2018 and had recruited 39 patients by January 2019. Results are expected by mid-2021.

In South Asia, with 126 patients enrolled in three sites in India (KAMRC and RMRI) and Bangladesh (icddr,b), recruitment has been completed in DND*i*'s Phase II study to assess the safety and efficacy of liposomal amphotericin B monotherapy and a combination of liposomal amphotericin B and miltefosine.

In addition, PKDL has long been thought to play an important role in transmission during outbreaks or during inter-epidemic periods, as PKDL lesions may be infectious to sandflies. In South Asia, the results of an infectivity study conducted in Bangladesh in 65 patients confirmed that PKDL acts as a reservoir for leishmaniasis infection.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

LSHTM Research Online

Quantifying the infectiousness of post-kala-azar dermal leishmaniasis towards sandflies. Clinical Infectious Diseases.

Mondal, Dinesh; Bern, Caryn; Ghosh, Debashis; Rashid, Masud; Molina, Ricardo; Chowdhury, Rajashree; Nath, Rupen; Ghosh, Prakash; Chapman, Lloyd; Alim, Abdul; Bilbe, Graeme; Alvar, Jorge

July 2019

To assess long-term infectivity and the impact of treatment, the study protocol was amended to repeat xenodiagnosis with PKDL patients after treatment completion. In Sudan, preparation for a similar infectivity study is underway.

Miltefosine+paromomycin combination for East Africa

Objective: Compare the efficacy and safety of two combination regimens of miltefosine and paromomycin with the current standard treatment

Based on the good results of the miltefosine and paromomycin (MF+PM) combination in South Asia, and on the need for an alternative and safer treatment to replace SSG, a Phase III study was launched in 2018 to compare two combination regimens of MF+PM with the current standard VL treatment, SSG+PM. The first patient in Sudan was enrolled in January 2018.

126 patients, both children and adults, were enrolled in five sites in Sudan, Kenya, Ethiopia, and Uganda by January 2019. Two additional sites in Sudan were scheduled for initiation in early 2019.

New VL treatments in Latin America

Objective: Assess the safety and efficacy of safer alternatives to the current standard VL treatment in Brazil

First-line treatment recommendations in Brazil include the use of meglumine antimoniate (MA), which presents serious patient management limitations due to toxicity, parenteral administration, and the need for hospitalization.

Starting in 2011, a multicentre, randomized, open label, controlled trial was conducted in five sites in Brazil to evaluate efficacy and safety of various treatment options, compared to standard treatment with MA.

Results showed that due to lower toxicity and acceptable efficacy, liposomal amphotericin B would be a more suitable first-line treatment for VL than standard treatment. The Brazilian Ministry of Health is currently reviewing its treatment policy to consider adoption of liposomal amphotericin B as the country's first-line VL treatment.

Delivered

SSG+PM for East Africa

Treatment options for visceral leishmaniasis in Africa had considerable limitations: liposomal amphotericin B was very costly and antimonials such as sodium stibogluconate had lengthy treatment times, difficult administration, emerging resistance, and poor tolerability that caused frequent side effects.

DND*i* partnered with the Leishmaniasis East Africa (LEAP) Platform in clinical trials that showed the combination of sodium stibogluconate and paramomycin (SSG+PM) was as safe and effective as the existing standard treatment. With SSG+PM, treatment is easier for patients and health centres, and it means more patients can be treated during outbreaks. Since 2010, SSG+PM has been recommended by WHO as first-line treatment for visceral leishmaniasis in East Africa, and PM has been registered in Kenya, Uganda, Sudan, and Ethiopia.

KalaCORE, the UK Aid-funded partnership that included DND*i* and supported the control and elimination of visceral leishmaniasis in six countries, supported the implementation of SSG+PM in East Africa. Access has been considerably improved thanks to the strengthening of the national control programmes of Ethiopia, South Sudan, and Sudan, and regular supply and distribution of diagnostics and medicines.

DND*i* continues to accompany the implementation of this treatment in East Africa.

Delivered

New visceral leishmaniasis treatments for South Asia

In the early 2000s, treatments for visceral leishmaniasis in South Asia were difficult for patients to take or were growing ineffective. Resistance was increasing, and antimonials such as sodium stibogluconate had lengthy treatment times, difficult treatment administration, and poor tolerability. In 2010, WHO recommended using new short-course treatments for visceral leishmaniasis in South Asia based on excellent results in Phase III studies. However, more evidence was needed on their safety and effectiveness under field conditions.

DND*i* convened a consortium of partners to identify the best combination therapies for South Asia. The consortium conducted a four year-long implementation study in Bangladesh and India to assess the safety, efficacy, and patient compliance of three new treatment options including single-dose liposomal amphotericin B, paromomycin and miltefosine, and liposomal amphotericin B and miltefosine combinations.

The results showed that these treatments were safe and effective, with cure rates above 95%. They also shortened treatment length, reduced the risk of resistance, and reached patients closer to home, making it easier for patients to take the full treatment course.

The research provided key evidence for policy change by the Bangladeshi, Indian, and Nepali Ministries of Health, which made the following recommendations: single-dose liposomal amphotericin B as a first-option treatment for visceral leishmaniasis patients, and paromomycin and miltefosine as a second option.

DND*i* continues to accompany the implementation of these new treatment options for VL in South Asia.

CHAGAS DISEASE

DND*i* aims to deliver new, safer, more affordable and effective treatments for people affected by Chagas disease. DND*i* is also focused on improving access to diagnosis and treatment using existing tools.

DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
Screening	Chagas Hit-to-lead	Chagas C205 Series ⊕	Biomarkers		Fexinidazole ⊕	New benznidazole regimens ⊕		**Benznidazole** paediatric dosage forms
	NTD Drug Discovery Booster Hit-to-lead							
	Daiichi Sankyo Hit-to-lead							

⊕ New chemical entity

June 2019

Screening

Objective: Deliver a robust portfolio of early hits and lead series to enable drug discovery for Chagas disease

To identify new hit series that could be progressed and become new drug candidates for Chagas disease, DND*i* tests chemical compounds for activity against *Trypanosoma cruzi*. High-throughput screening of compounds from collections from partners or commercial suppliers have been conducted, and hits have been identified and are currently being progressed.

Hit-to-lead

Objective: through collaborative hit-to-lead projects, identify new leads with activity in animal models of disease and the potential for further optimization

The aim is to improve hits from *in vitro* screening through cycles of design, chemical synthesis, and testing to generate leads with activity in animal models of Chagas disease that can then be further optimized. Projects include:

- DND*i* is working on a series known as **'C205/220'** in late-lead optimization phase, as part of a collaboration agreement made in 2018 with the Drug Discovery Unit from the Dundee University in Scotland (DDU) and the Global Health unit within GlaxoSmithKline in Spain. Work on the series has been focusing on safety profiling and exploratory toxicology for the selected front-runners.
- Through the **NTD Drug Discovery Booster** project, DND*i* brings together pharmaceutical companies in a non-competitive search process to speed up and the process and cut the cost of finding new treatments for Chagas disease. The project conducts multilateral, simultaneous searches of millions of compounds based on an active seed supplied by DND*i* and uses computational approaches to refine the search iteratively. In 2018, the Japanese pharmaceutical company Astellas Pharma Inc. became the eighth company to join the consortium (after AbbVie, AstraZeneca, Celgene, Eisai, Merck, Shionogi, and Takeda). Since its creation in 2015, the Booster has launched 45 iterations around 22 seed compounds, with the result that 13 hit series have been released, of which six have progressed to *in vivo* proof-of-concept studies for Chagas disease and/or leishmaniasis.
- DND*i* partnered with Japanese pharmaceutical company **Daiichi Sankyo** in a hit-to-lead project that ended in September 2018. The project milestone was reached with the identification of a progressable Chagas lead series with proven *in vivo* efficacy. Daiichi Sankyo and DND*i* are now looking for funding to progress this promising series for Chagas disease in 2019.

Biomarkers

Objective: Identify and evaluate new biological markers of therapeutic efficacy in chronic Chagas disease

There is no single reliable test of cure that can be used to monitor the efficacy of a treatment in chronic Chagas disease patients in a timely manner. This lack of validated early markers of serological cure poses a significant hurdle for the development and regulatory approval of new drugs.

Current work focuses on raising awareness among Chagas stakeholders about the need for biomarkers, with particular emphasis on regulatory aspects and the biomarker development process. In parallel, DND*i* is supporting the development of a prototype assay for newly identified biomarkers – Apo A1 and Fbn fragments issued from a collaboration with McGill University – with InfYnity Biomarkers.

The analysis of a multi-centric study carried out by NHEPACHA, an Ibero-American network of researchers working on Chagas, aimed at establishing the predictive value of therapeutic efficacy

of different biomarkers, was discussed at the XV Chagas Disease Workshop in March 2019.

New benznidazole regimens

Objective: Evaluate new therapeutic regimens of benznidazole as monotherapy, or in combination with fosravuconazole, for the treatment of adult patients with chronic Chagas disease

Current Chagas treatment is effective but has limitations: it lasts 60 days, and some 20% of patients stop treatment due to side effects, which include gastric intolerance, skin rashes, or neuromuscular problems. To explore whether these were related to dose or treatment duration, DND*i* decided to test the efficacy of new regimens where exposure to benznidazole would be reduced, either due to shorter treatment, lower doses, or both. The objective of the BENDITA study (Benznidazole New Doses Improved Treatment & Therapeutic Associations) was to find regimens at least as effective as the standard treatment, with fewer side effects. This could improve patients' adherence and make the treatment more acceptable to physicians.

A Phase II, randomized, placebo-controlled study was carried out in three sites in Bolivia between 2016 and 2018. It tested, against a placebo, six benznidazole treatments of differing lengths and dosages, both as a monotherapy and in combination with fosravuconazole, a new chemical entity owned by Eisai. The aim was to improve efficacy, safety, and tolerability of treatment of adults with chronic indeterminate Chagas.

The results, available in early 2019, showed that all treatment arms were effective compared to placebo and the new regimens presented good safety profiles. The two-week course of treatment was particularly promising. While significantly shorter than the standard eight-week treatment, it showed 83% of efficacy and none of the patients assigned to this arm had to discontinue treatment due to side effects. The primary measure of efficacy for this study was sustained parasitological response at six months' follow-up with a final assessment at 12 months.

DND*i* will now continue to work with national programmes, partners, and health ministries of endemic countries to confirm these results and encourage the necessary steps to register the new regimen.

Analysis of parositological response at 6-month follow-up and 12-month follow-up*

	BZN 300 mg 8 wks	BZN 300 mg 4 wks	BZN 300 mg 2 wks	BZN 150 mg 4 wks	BZN 150 mg 4 wks/E1224 300 mg	BZN 300 mg (Weekly) 8wks/ E1224 300 mg	Placebo
6-months follow-up	89.3 %	89.3%	82.8%	83.3%	85.2%	82.8%	3.3%
12-months follow-up	82.8%	89.3%	79.3%	80.0%	85.2%	82.8%	3.3%
Subject with treatment-related side effects leading to treatment discontinuation	6 (20.0%)	1 (3.3%)	0	1 (3.3%)	3 (10.0%)	4 (13.3%)	0%

* *Intention to treat analysis, meaning that all patients enrolled in the study and randomized to a treatment arm were included in the analysis, whether or not they started or completed treatment.*

Fexinidazole

Objective: Evaluate efficacy and safety of short-course and low-dose regimens of fexinidazole in adults with chronic Chagas disease

While fexinidazole was registered as a drug to treat sleeping sickness in 2018, DND*i* is also exploring its potential as a new drug for Chagas disease.

By September 2018, recruitment of 45 patients had been completed in a Phase II proof-of-concept study carried out in five sites in Spain to test different short-course regimens of fexinidazole for adults with chronic indeterminate Chagas. The study is now in the follow-up phase and will be completed in late 2019, with results available in 2020.

If the decision is taken to proceed to a Phase III trial and fexinidazole is shown to be effective, it would be the first new drug to treat Chagas disease in more than 50 years.

Delivered

Two sources of paediatric benznidazole

Until 2011, benznidazole, the main drug of choice for treating Chagas disease, was only available in an adult-strength tablet. Infants and children were treated with divided or crushed adult tablets, which was complicated for caregivers and resulted in inconsistent dosing.

A first paediatric formulation was developed through a collaboration between DND*i* and Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE) of Brazil and was registered in 2011, in Brazil. A second paediatric benznidazole source was registered in Argentina in 2018, the result of a partnership between Fundación Mundo Sano, DND*i* and Laboratorio Elea Phoenix to enable a stable supply and registration in additional disease-endemic countries.

Chagas Access Project

Objective: Demonstrate the feasibility of scaling up access to diagnosis and treatment in pilot projects that can then be replicated on a larger scale

In 2015, DND*i* launched an initiative to increase access to diagnosis and treatment to Chagas disease in close collaboration with local, regional, and national partners through pilot projects in several endemic countries.

The approach was first implemented in Colombia in collaboration with the Ministry of Health and Social Protection, targeting a highly endemic area for Chagas disease. The new patient-centred approach involves training health care staff, simplifying, and accelerating the procedure for diagnosis, and decentralizing treatment to ensure it is available closer to where patients live. In the two communities where the pilot was first implemented, 384 people were tested for Chagas disease in the first year, a ten-fold increase over the previous year. Wait times for diagnostic confirmation were reduced from an average of 364 to just 17 days, and there was a four-fold increase in the number of patients starting etiological treatment. In 2018, the Colombian project expanded to additional communities.

The positive experience and promising results of the Colombia project led to the development of a collaborative project in the U.S. focused on advancing public health research on Chagas disease, including the first large-scale prevalence study in a major U.S. city in 2017.

Projects were also launched along the same model in Guatemala with local and international partners, and in Brazil in partnership with the Oswaldo Cruz Foundation. Seminars were held in Jutiapa, Guatemala, and in Rio de Janeiro and Recife, Brazil to identify the main barriers and develop actions to strengthen disease control and treatment access.

MYCETOMA

DND*i* aims to develop an effective, safe, affordable, and simpler curative treatment. There is currently no effective cure for fungal mycetoma.

DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
						Fosravuconazole ⊕		

⊕ New chemical entity

June 2019

MycetOS

Objective: Use an open source approach to discover compounds that could lead to new treatments

In February 2018, the Mycetoma Open Source (MycetOS) project was launched by the University of Sydney, Australia, Erasmus MC (Erasmus University Medical Center, Rotterdam, the Netherlands), and DND*i* to use an 'Open Pharma' approach to discover compounds that could lead to new treatments for patients suffering from fungal mycetoma (eumycetoma).

MycetOS will progress drug discovery efforts through community-driven, in-kind scientific contributions and a robust, fully transparent online presence. All ideas and results will be published immediately in real time to an open-access database.

Results and the associated data form the starting point for the MycetOS community, which communicates on Twitter (@MycetOS) and uses a dedicated forum (subreddit) for transparent interactive discussion, and another platform (github) for sharing data and key project files.

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Addressing the most neglected diseases through an open research model: The discovery of fenarimols as novel drug candidates for eumycetoma

Wilson Lim, Youri Melse, Mickey Konings, Hung Phat Duong, Kimberly Eadie,Benoît Laleu, Benjamin Perry, Matthew H. Todd, Jean-Robert Ioset, Wendy W. J. van de Sande

April 2018

Fosravuconazole

Objective: Study the efficacy of fosravuconazole as a potential new, safe, and affordable treatment for patients with eumycetoma

In 2017, the Mycetoma Research Centre (MRC), a WHO Collaborating Centre, in Khartoum, Sudan, began enrolling patients in the first-ever double-blind, randomized clinical trial for eumycetoma (fungal mycetoma).

The trial is studying the efficacy, in moderate-sized lesions over 12 months, of weekly treatment with fosravuconazole, versus the current standard of care, daily treatment with itraconazole.

Fosravuconazole, an orally bioavailable azole developed for onychomycosis by Eisai Ltd (Japan), could be an effective and affordable treatment for eumycetoma. Its pharmacokinetic properties are favourable, and its toxicity is low. Fosravuconazole is also being evaluated by DND*i* for Chagas disease.

Following slower than anticipated patient enrolment, a protocol review and amendment was conducted in 2018 to extend the inclusion criteria in relation to lesion size and site, as well as the age range of participants. By January 2019, 84 patients had been enrolled, reaching the threshold for interim analysis. The analysis will determine which of the two treatment arms (a weekly dose of 200 mg or 300 mg of fosravuconazole) will be retained for the remainder of the trial.

FILARIAL DISEASES

DND*i* aims to deliver a safe, effective, affordable, and field-adapted drug that can kill adult filarial worms (a 'macrofilaricide') and be used for prevention or individual treatment.

DISCOVERY			TRANSLATION		DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
Screening		Macrofilaricide 3 ⊕		Oxfendazole ⊕	Emodepside ⊕			
					TylAMac (ABBV-4083) ⊕			

⊕ New chemical entity

June 2019

Screening

DND*i*'s filarial disease programme actively identifies potential new drug candidates for onchocerciasis by evaluating registered drugs, as well as pre-clinical and clinical drug candidates. DND*i* also investigates diverse chemical compounds against filarial worms. Well-characterized libraries of compounds that had already been extensively optimized for other indications were provided to DND*i* by several pharmaceutical companies for screening. Some 530 compounds have now been screened in partnership with Salvensis, Merck Sharp & Dohme, University of North Carolina, AbbVie, and others.

From this initial screen, a full lead optimization programme to further develop these compounds has been undertaken in collaboration with Celgene, with additional exploration of identified 'hits'. This effort will continue, with the aim of delivering several backup drug candidates for filarial diseases.

Macro-filaricide 3

Objective: Develop a macrofilaricide candidate for filarial diseases

Lead optimisation of a novel class of compounds with macro-filaricidal profiles is on-going, with the aim of selecting a candidate for pre-clinical development in 2019.

Emodepside

Objective: Advance the clinical development of emodepside as an anti-parasitic macrofilaricidal treatment

Originating from the Japanese pharmaceutical company Astellas, emodepside was developed and commercialized by Bayer Animal Health as a veterinary drug for parasitic worm infections in cats and dogs. DND*i* has a collaboration agreement with Bayer AG to jointly develop emodepside for the treatment of onchocerciasis. Bayer provides the active ingredient emodepside to DND*i*, and DND*i* is responsible for the clinical development of emodepside and Bayer for the pre-clinical and pharmaceutical development, as well as for registration, manufacturing, and distribution of the drug.

First-in-human studies for emodepside in healthy volunteers have successfully been completed, both a single ascending dose study in 2017 and a multiple ascending dose study in 2018. Emodepside is orally bioavailable and a tablet that could be commercialized has been developed.

As a next step, DND*i* plans to run a Phase II proof-of-concept clinical trial in DRC and Ghana, investigating the safety and efficacy of the drug in people living with onchocerciasis.

TylAMac (ABBV-4083)

Objective: Advance the clinical development of TylAMac as a macrofilaricidal treatment that targets *Wolbachia* bacteria

The filaria causing river blindness are dependent on the worm-symbiont *Wolbachia* bacteria for growth, development, reproduction, and survival; elimination of the symbiont with antibiotic drugs therefore has the potential to lead to worm death, delivering a new and practical solution for treating and eliminating this deadly disease.

TylAMac, or ABBV-4083, is a derivative of tylosin, a veterinary antibiotic that targets *Wolbachia*, and was identified by a screening of anti-infective compounds led by AbbVie and the anti-*Wolbachia* consortium A-WOL at the Liverpool School of Tropical Medicine.

The compound is currently in clinical development for the treatment of filarial diseases. ABBV-4083 is orally available, induces a robust anti-*Wolbachia* effect in several *in vivo* models, demonstrates clear superiority over doxycycline, and is effective after a shorter dosing regimen.

Toxicology studies were completed in 2017 and an oral formulation was developed. In December 2017, AbbVie began the first human trial of TylAMac to test the drug's safety in healthy volunteers and assist in the selection of doses for future trials. This Phase I study took place at AbbVie's Clinical Pharmacology Research Unit and was completed in 2018.

The results support progression to Phase II. As a next step, DND*i* plans to run a Phase II proof-of-concept clinical trial in sub-Saharan Africa, investigating the safety and efficacy of the drug in people living with onchocerciasis.

Oxfendazole

Objective: Advance the clinical development of oxfendazole as an anti-parasitic macrofilaricidal treatment

Screening of drug libraries obtained from biotech and pharmaceutical companies, along with active screening of the literature, identified oxfendazole, a veterinary product used for deworming in animals, as a potential candidate macrofilaricidal agent for river blindness.

Oxfendazole is currently under development for the treatment of neurocysticercosis and trichuriasis. Based on very encouraging pre-clinical efficacy data, DND*i* is exploring the possibility of repurposing oxfendazole as a macrofilaricidal treatment for filarial indications.

DND*i* is moving ahead with a first-in-human Phase I trial and pharmaceutical development.

PAEDIATRIC HIV

DND*i* aims to help end the neglect of paediatric HIV by developing optimal child-friendly antiretroviral formulations for children living with HIV, with a special focus on infants and young children who are at the highest risk of dying without treatment.

DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
						4-in-1 (ABC/3TC/LPVr)		**Super-booster therapy** for children with HIV/TB
								2-in-1 LPV/r pellets and ABC/3TC or AZT/3TC

⊕ New chemical entity

June 2019

'4-in-1' ABC/3TC/LPV/r

Objective: Develop and register a solid, taste-masked, first-line LPV/r-based fixed-dose formulation with two nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine and abacavir

Building on the work on increasing access to better formulations for children living with HIV *(see below on the '2-in-1')*, a first-line '4-in-1' fixed-dose combination of abacavir/lamivudine/lopinavir/ritonavir (ABC/3TC/LPV/r) is on track to be submitted for registration by Cipla Ltd. (India) in 2019.

The 4-in-1 will be simple to use with water, milk, breast milk, and food. It will be taste-masked and heat-stable – a great improvement over the current option, a paediatric syrup of lopinavir/ritonavir (LPV/r) with high-alcohol content.

To provide clinical data in young HIV-infected infants and children, DND*i* is preparing a study, called LOLIPOP, to assess this 4-in-1 combination as an easy-to-use paediatric formulation in a Phase I/II study. The LOLIPOP study, which has received ethical approval, began in 2019 in Uganda and will generate pharmacokinetic, safety, and acceptability data on the 4-in-1 to provide evidence for worldwide scale-up.

'2-in-1' LPV/r pellets, with dual NRTI

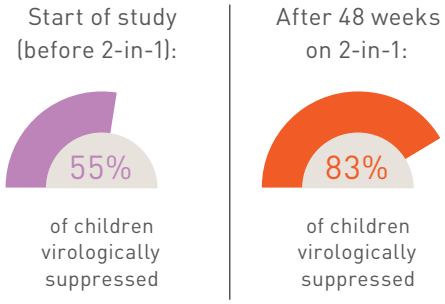
Objective: Evaluate the effectiveness of LPV/r pellets, given with two NRTIs (either AZT/3TC or ABC/3TC), in an implementation study in HIV-infected infants and young children who cannot swallow pills

In 2015, following the tentative approval by the US FDA of the lopinavir/ritonavir (LPV/r) 2-in-1 pellets developed by Cipla Ltd. (India), DND*i* launched the LIVING study in five sites in Kenya to provide early access to the new formulation. The pellets are taken orally and are a significant improvement over the high-alcohol, bitter-tasting and refrigerated syrups that were previously the only available LPV/r formulation for young children. The study was expanded to Uganda in 2016 and Tanzania in 2017.

As of December 2018, the LIVING study had enrolled 1,003 children across 12 sites in Kenya, Uganda, and Tanzania, and follow-up was completed for the Kenyan and Ugandan sites.

In February 2018, interim results of the LIVING study were released, showing that 83% of the children were virologically suppressed at 48 weeks with the 2-in-1, compared to 55% at the beginning of the study. These results show that the 2-in-1 is effective and well-tolerated by children.

LIVING study interim results



DND*i* is now actively preparing to build on the work on the 2-in-1 to facilitate transition and support access to the 4-in-1, once it is registered.

Delivered

Super-booster therapy for paediatric HIV/TB

Objective: Support implementation of and access to a stand-alone pharmacokinetic ritonavir booster formulation, to be added to any protease inhibitor-based paediatric ARV regimen for the treatment of HIV/TB co-infected children.

Rifampicin, the backbone of the regimen to treat tuberculosis (TB) in children, reduces the bioavailability of protease inhibitors such as lopinavir/ritonavir (LPV/r). This negative drug-drug interaction is a major challenge in treating children infected with both HIV and TB.

As part of its development of protease inhibitor-based antiretroviral regimens for children, DND*i* carried out a pharmacokinetic study in 96 infants and young children co-infected with HIV and TB at five sites in South Africa. The objective was to demonstrate the safety and effectiveness of 'super-boosting', which involves adding extra ritonavir to the LPV/r regimen in order to counter this drug-drug interaction.

The results were presented to the WHO guidelines review committee and have strengthened the WHO recommendation to super-boost ritonavir in HIV/TB co-infected children on an LPV/r-based therapy. This study has been completed and final results were presented in 2017 and published in 2018, showing that super-boosting is safe and effective. This work will greatly facilitate similar investigations with the 4-in-1 for the treatment of young children co-infected by HIV and TB.

THE LANCET HIV

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

Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S, Liberty A, Simon F, McIlleron H, Cotton MF, Lallemant M

January 2019

HEPATITIS C VIRUS (HCV)

DND*i* aims to deliver:

- A safe, effective, and easy-to-use direct-acting antiviral regimen, to be used as an affordable combination paving the way for a public health approach to HCV.
- Increased access to affordable treatments by supporting policy change and encouraging political will to treat HCV.
- Innovative programmes to improve access to HCV diagnosis and treatment in a variety of countries.

DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screening	Hit-to-lead	Lead optimization	Pre-clinical	Phase I	Phase IIa/ Proof-of-concept	Phase IIb/III	Registration	Treatment access
						Ravidasvir + sofosbuvir ⊕	Ravidasvir ⊕	

⊕ New chemical entity

June 2019

A public health approach to reverse the epidemic

In addition to R&D, DND*i*'s HCV programme includes work with MSF to develop and implement simpler models of care, well as in large-scale treatment cohorts in Cambodia.

The objective is to demonstrate that the challenges posed by HCV can be addressed through a public health approach.

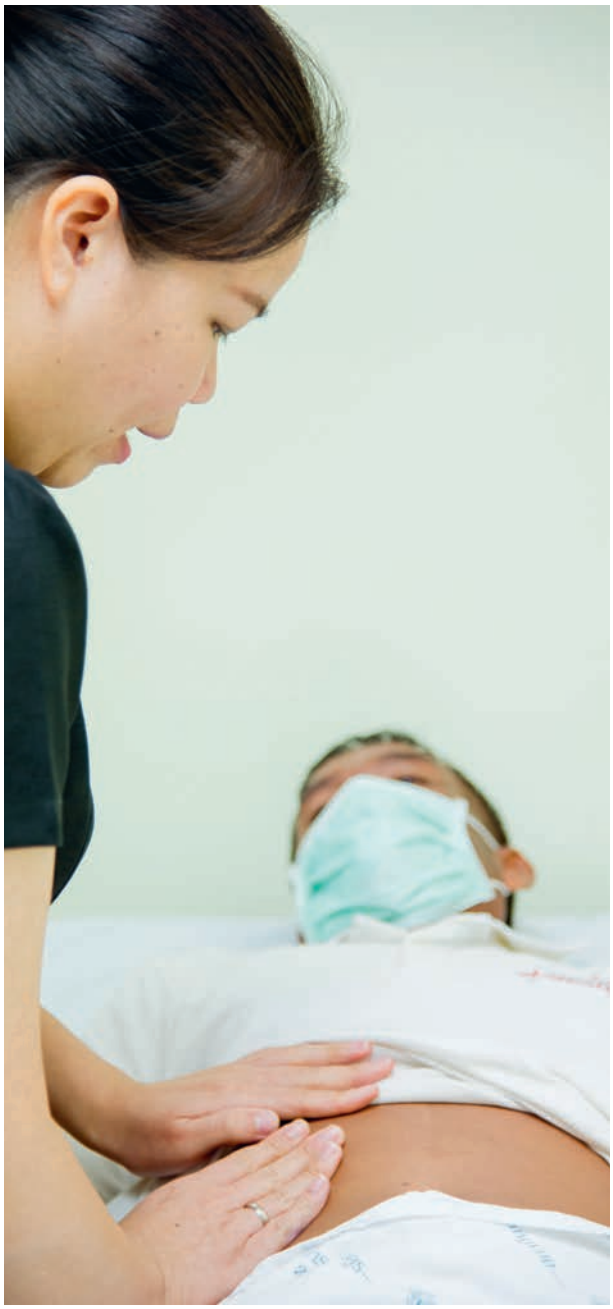
The widespread use of affordable, safe, and effective direct-acting antivirals would enable a public health approach to the epidemic: if people are diagnosed and treated early enough to avoid infecting others, the disease could actually be eliminated globally, as planned by WHO. Yet very few patients have access to diagnosis and treatment, notably due to high treatment prices.

An affordable pan-genotypic combination would benefit many patients, particularly in countries that are excluded from licensing agreements that enable access to generic HCV treatments, and in which generic competition is not sufficiently robust to bring prices down.

Working together to find the missing millions

In July 2018, DND*i* and diagnostic product development and delivery partnership FIND announced a partnership, in collaboration with the Ministry of Health in Malaysia, to generate evidence to support policy change and scale up HCV diagnosis and treatment.

As a part of the project, simplified decentralized screening for HCV has been initiated in Malaysia. People who screen positive and are subsequently confirmed to have HCV are linked to treatment either in government hospitals or, on a voluntary basis, as part of the DND*i* clinical trial.



Ravidasvir + sofosbuvir

Objective: Conduct Phase II/III clinical trials to evaluate the efficacy of a ravidasvir + sofosbuvir combination

Ravidasvir (RDV) was developed by the US biopharmaceutical company Presidio and identified by DND*i*. In 2016, Presidio, DND*i*, and the Egyptian generic manufacturer Pharco signed a licence agreement to secure supplies of RDV and of sofosbuvir (SOF).

In 2016, DND*i* launched a Phase II/III study in Malaysia and Thailand to assess the efficacy, safety, tolerability, pharmacokinetics, and acceptability of 12- and 24-week regimens containing the drug candidate RDV, in combination with SOF, for people living with hepatitis C.

The trial was co-sponsored by the Malaysian Ministry of Health and co-financed by Médecins Sans Frontières (Doctors Without Borders, or MSF). A total of 301 patients were included: 220 in Malaysia and 81 in Thailand. Patients were included regardless of HIV co-infection status, as were people with compensated liver disease with or without cirrhosis.

Interim results published in April 2018 (see box) showed that 12 weeks after the end of treatment, 97% of the 301 patients enrolled were cured (95% CI: 94.4-98.6). Cure rates were very high even for the hardest-to-treat patients. Importantly, patients combining several risk factors were cured, and no unexpected safety signals were detected.

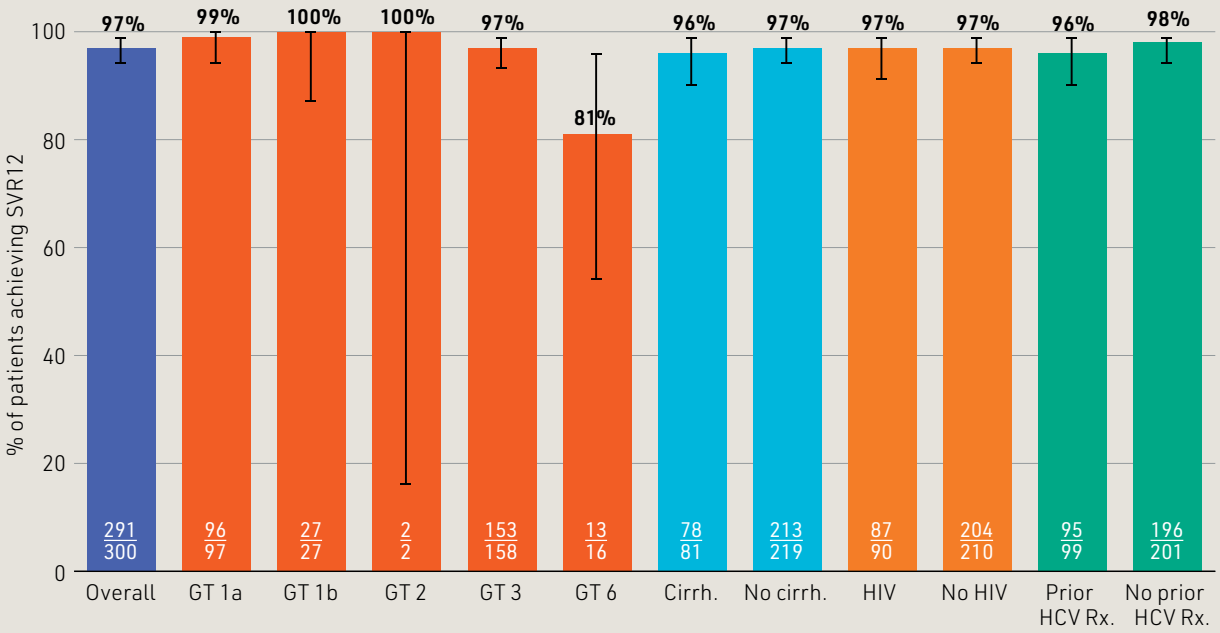
To further establish the pan-genotypic profile of RDV, the second stage of the trial was launched in December 2018 in Malaysia and in Thailand in May 2019. Other trials are envisioned in other parts of the world, for vulnerable patient groups, such as people who use drugs.

Registration of RDV will be pursued in Malaysia and other middle-income countries, including in Argentina, with DND*i*'s pharmaceutical partners Pharmaniaga and Elea Phoenix, respectively.

DND*i* signed a technology transfer agreement with Pharco (Egypt) and Pharmaniaga in late 2017.

STORM-C-1 TRIAL
SUSTAINED VIRAL RESPONSE 12 WEEKS AFTER END OF TREATMENT (SVR 12) - INTERIM RESULTS

Outcomes in intention-to-treat analysis with full analysis set



GT = genotype; Cirrh. = cirrhosis; No cirrh. = no cirrhosis; Rx = treatment

Main R&D Partners*

Sleeping sickness

Accelera, Italy; Advinus Therapeutics Ltd, India; Aesica, UK; Amatsi Aquitaine (formerly Bertin Pharma), France; Analyticon Discovery Gmbh, Germany; Aptuit, Italy; Asinex Corporation, United States; Avista Pharma (formerly SCYNEXIS), USA; Biotrial, France; Bureau d'Etude d'Ingénierie -Ste Dina Sarl, Guinea; Cardiabase, France; CBCO, DR Congo; Centipharm, France; Creapharm, France; Drugabilis, France ; Eurofins-Optimed, France; HAT Platform; Institut de Recherche pour le Développement, France; Institut National de Recherche Biomédicale, DR Congo; Institute of Tropical Medicine Antwerp, Belgium; Laboratoire La Reference, Guinea; Laboratory of Microbiology, Parasitology, and Hygiene, University of Antwerp, Belgium; Luxembourg Institute of Health, Luxembourg; Médecins Sans Frontières; National Control Programmes of the Democratic Republic of Congo, the Central African Republic, and of Guinea; Pace University, USA; Patheon, UK; Pfizer Inc., USA; Pfizer Inc. (formerly Anacor Pharmaceuticals Inc.), USA; PhinC, France; RCTs, France; Sanofi, France; SGS, Belgium; SGS, France; Swiss Tropical and Public Health Institute, Switzerland; Theradis Pharma, France; Trade Factors Overseas Ltd, Great Britain; WHO-NTD (Neglected Tropical Diseases department).

Leishmaniasis

AbbVie, USA; Accelera, Italy; Academic Medical Center in Amsterdam, the Netherlands; Addis Ababa University, Ethiopia; Advinus Therapeutics Ltd, India; Amatsi Aquitaine (formerly Bertin Pharma), France; Amc Medical Research B.V, the Netherlands; Amudat Hospital, Uganda; Aptuit, Italy; Analysis Ltd R.A.K, United Arab Emirates; Astellas Pharma Inc., Japan; AstraZeneca, Sweden and UK; Auckland University, New Zealand; Banook group, France; BaseCon, Denmark; Bayer, Germany; Bioascent, UK; BioAster, France; Bio Zeq Kenya Ltd, Kenya; Brasilia University, Brasilia, Brazil; Bristol-Myers Squibb, USA; Celgene Corporation, USA; Centre for Drug Candidate Optimisation, Monash University, Australia; Centro National de Pesquisa em Energia e Materiais (CNPEM), LN Bio, Brazil; Charles River Laboratories (Wil Research), France and the Netherlands; Crystallise!, Switzerland; Daiichi Sankyo Company, Limited, Japan; Daiichi Sankyo RD Novare Co., Ltd, Japan; Drug Discovery Unit, University of Dundee, UK; EI du Pont de Nemours, USA; Eisai Co., Ltd., Japan; Epichem, Australia; Eurofins Cerep, France; Eurofins Panlabs Thailand, Thailand; Eurofins Panlabs, USA; Eurofins-Optimed, France; Foundation for Innovative New Diagnostics, Switzerland; GeneDesign Inc., Japan; Gilead Sciences, USA; GlaxoSmithKline, Spain and UK; Gondar University Hospital, Ethiopia; Griffith Institute for Drug Discovery, Griffith University, Australia; Hospital Sao José de Doencas Infecciosas, Fortaleza; Hypha Discovery Ltd, UK; Iktos, France; Institut Pasteur Korea, South Korea; Institute of Endemic Disease, Khartoum University, Sudan; Institute of Medical Sciences, Banaras Hindu University, India; Institute of Microbial Chemistry, Japan; Institute of Tropical Medicine Antwerp, Belgium; Instituto de Ciencias Biomedicas, Universidade de Sao Paulo, Brazil; Instituto de Física, Universidade de São Paulo, Brazil; Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru; Instituto de Química, Universidade Estadual de Campinas, Brazil; Instituto de Salud Carlos III, Spain; International Centre for Diarrhoeal Disease Research, Bangladesh; Johnson & Johnson, USA; Kacheliba District Hospital, Kenya; Kala Azar Medical Research Centre, India; Kenya Medical Research Institute, Kenya; Kitasato Institute for Life Sciences, Japan; Laboratory of Microbiology Parasitology and Hygiene, University of Antwerp, Belgium; Lambda Therapeutic Research Ltd., India; LEAP Platform; London School of Hygiene & Tropical Medicine, UK; Makerere University, Uganda; Médecins Sans Frontières, Spain; Médecins Sans Frontières, the Netherlands; Medicines for Malaria Venture, Switzerland; Merck KGaA, Germany; Merck, USA; Ministry of Health, Neglected Tropical Disease Directorate, Ethiopia; Ministry of Health, Neglected Tropical Diseases Unit, Leishmaniasis Programme, Kenya; Ministry of Health, Neglected Tropical Diseases Unit, Leishmaniasis Programme, Sudan; Ministry of Health, Leishmaniasis Control Programme, Uganda; Montes Claros State University, Montes Claros, Brazil; Nagasaki University, Japan; National Institute of Pathology, India; National Institutes of Health, USA; Netherlands Cancer Institute, the Netherlands; Nki Stichting Het Nerderland Kander Instituut, the Netherlands; Northwick Park Institute for Medical Research, UK; Novartis, Switzerland and USA; Ohio State University, USA; Osaka University, Japan; Paediatric Hospital Joao Paulo II – FHEMIG, Belo Horizonte, Brazil; Pentlands Management Systems Ltd, United Kingdom; Pkpdesign Sas, France; Pfizer Inc., USA; Pfizer Inc. 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Chagas disease

AbbVie, USA; Astellas Pharma Inc., Japan; AstraZeneca, Sweden and UK; Barcelona Centre for International Health Research (CRESIB), Spain; Barcelona Centre for International Health Research, Spain; Barcelona Institute for Global Health (ISGlobal), Spain; Bayer, Germany; Bioascent, UK; Bioaster, France; Brazilian Biosciences National Laboratory, Brazil; Bristol-Myers Squibb, USA; Broad Institute of M.I.T and Harvard, USA; CEADES, Bolivia; Celgene Corporation, USA; Centre for Drug Candidate Optimisation, Monash University, Australia; Center of Excellence for Chagas Disease, United States; Centro de Chagas y Patologia Regional, Hospital Independencia, Argentina; Centro National de Pesquisa em Energia e Materiais, LN Bio, Brazil; Chembridge Corporation, United States; Collective of Applied Studies and Social Development, Bolivia; Daiichi Sankyo Company, Limited, Japan; Daiichi Sankyo RD Novare Co., Ltd., Japan; Drug Discovery Unit, University of Dundee, UK; EI du Pont de Nemours, USA; Eisai Co., Ltd., Japan; Exeltis, USA; Epichem, Australia; Eurofins, France; FP Clinical Pharma – Ethel Feleder, Argentina; Fundacio Investigacio Hospital General Valencia, Spain; Fundación Instituto de Investigaciones Biotecnológicas, Argentina; Hospital Universitario La Paz, Spain; GlaxoSmithKline, Spain and UK; Griffith Institute for Drug Discovery (GRIDD), Griffith University, Australia; Hospital Clínic de Barcelona, Spain; Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; Hospital General de l'Hospitalet Consorci Sanitari Integral, Barcelona, Spain; Infectious Diseases Data Observatory, University of Oxford, UK; Infynity

*Partners listed here include partners involved since the start of the project; for projects, see DND*i*'s R&D portfolio (https://www.dndi.org/diseases-projects/portfolio/).

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Mycetoma

Eisai Co., Ltd., Japan; Erasmus Medical Center, the Netherlands; Free University Amsterdam, the Netherlands; Institute of Endemic Diseases, Khartoum University, Sudan; Mycetoma Research Centre, Soba University Hospital, Khartoum, Sudan; Radboud University Medical Center, Nijmegen, the Netherlands.

Filarial diseases

AbbVie, USA; AWOL, UK; Analytical Services International, UK; Bayer, Germany; Bonn University Hospital, Institute of Medical Microbiology, Immunology and Parasitology, Germany; Celgene Corporation, USA; Commissariat à l'énergie atomique et aux énergies alternatives, France; Erasmus Medical Center, the Netherlands; Hammersmith Medicines Research, UK; Imperial College, UK; Institut Bouisson Bertrand, France; Institut de Recherche pour le Développement, France; Liverpool School of Tropical Medicine, UK; Mahidol University, Thailand; Merck, USA; National Museum of Natural History, France; Niche Science and Technology, UK; Northwick Park Institute for Medical Research, UK; Research Foundation for Tropical Diseases and the Environment, Cameroon; Salvensis, UK; University of North Carolina, USA; University of Health and Allied Sciences, Ghana; University of Liverpool, United Kingdom; Washington University in St Louis, USA.

HIV

AMPATH, Kenya; AbbVie, USA; Associated Medical Sciences/PHPT International Research Unit, Thailand; Baylor College of Medicine Children's Foundation, Uganda; Centre for Disease Control and Prevention/President's Emergency Plan for AIDS Relief, USA; Cipla Ltd., India; Clinton Health Access Initiative, USA; Department of Health, South Africa; Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, South Africa; Enhancing Care Foundation, South Africa; Epicentre, Uganda; Family AIDS Care and Education Services Project, Kenya; Gertrude's Children's Hospital, Kenya; i-Base, UK; Ifakara Health institute, Tanzania; Institute of Tropical Medicine, Antwerp; International Community of Women Living with HIV, Kenya; Joint Clinical Research Centre, Uganda; Kenya Medical Research Institute, Kenya; Kenyatta National Hospital, Kenya; Management and Development for Health, Tanzania; Mbagathi District Hospital, Kenya; Médecins Sans Frontières; Medical Research Council, UK; Ministries of Health of Kenya, Tanzania, Uganda, and Zimbabwe; Moi Teaching and Referral Hospital, Kenya; Moi University, Kenya; Necker Institute, France; NEPHAK, Kenya; Nyumbani Lea Toto Project, Children of God Relief Institute, Kenya; Perinatal HIV Research Unit, University of Witswatersrand, South Africa; Shandukani Research Centre, Wits Reproductive Health and HIV Institute, South Africa; St Lumumba Health Centre, Kenya; Stellenbosch University and Tygerberg Children's Hospital, South Africa; Swiss Tropical and Public Health Institute, Switzerland; University of Nairobi, Kenya; various academic partners in South Africa, Kenya, Uganda, and Tanzania.

Hepatitis C

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2018 Scientific publications by DND*i* and GARDP

In 2018, DND*i* staff members authored or co-authored 26 peer-reviewed publications. Of these, 23 had a lead author or co-author from an endemic country, and 85% were published in an open access journal, in keeping with DND*i*'s commitment to open access.

DND*i*:

Kinetoplastid diseases

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Leishmaniasis

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PKDL development after combination treatment with miltefosine and paromomycin in a case of visceral leishmaniasis: First ever case report by Pandey K, Goyal V, Das VNR, Verma N, Rijal S, Das P, and Alvar J. *Journal of Medical Microbiology and Immunology Research*, February 2018

Development of (6R)-2-Nitro-6-[4-(trifluoromethoxy)phenoxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (DNDI-8219): A new lead for visceral leishmaniasis by Thompson AM, O'Connor PD, Marshall AJ, Blaser A, Yardley V, Maes L, Gupta S, Launay D, Braillard S, Chatelain E, Wan B, Franzblau SG, Ma Z, Cooper CB, and Denny WA. *Journal of Medicinal Chemistry*, February 2018

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Macrophage activation marker neopterin: A candidate biomarker for treatment response and relapse in visceral leishmaniasis by Kip AE, Wasunna M, Alves F, Schellens JHM, Beijnen JH, Musa AM, Khalil EAG, and Dorlo TPC. *Frontiers in Cellular and Infection Microbiology*, June 2018

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Field safety and effectiveness of new visceral leishmaniasis treatment regimens within public health facilities in Bihar, India by Goyal V, Mahajan R, Pandey K, Singh SN, Singh RS, Strub-Wourgaft N, Alves F, Das VNR, Topno RK, Sharma B, Balasegaram M, Bern C, Hightower A, Rijal S, Ellis S, Sunyoto T, Burza S, Lima N, Das P, Alvar J. *PLOS Neglected Tropical Diseases*, October 2018

Barriers to access to visceral leishmaniasis diagnosis and care among seasonal mobile workers in Western Tigray, Northern Ethiopia: A qualitative study by Coulborn RM, Gebrehiwot TG, Schneider M, Gerstl S, Adera C, Herrero M, Porten K, den Boer M, Ritmeijer K, Alvar J, Hassen A, Mulugeta A. *PLOS Neglected Tropical Diseases*, November 2018

Chagas disease

Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial by Torrico F, Gascon J, Ortiz L, Alonso-Vega C, Pinazo MJ, Schijman A, Almeida IC, Alves F, Strub-Wourgaft N, Ribeiro I. *The Lancet Infectious Diseases*, January 2018

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Dried blood spot technique-based liquid chromatography-tandem mass spectrometry method as a simple alternative for benznidazole pharmacokinetic assessment by Galindo Bedor DC, Tavares Cavalcanti Bedor NC, Viturino da Silva JW, Damasceno Sousa G, Pereira de Santana D, Garcia-Bournissen F, Altcheh J, Blum B, Alves F, Ribeiro I. *Antimicrobial Agents and Chemotherapy*, October 2018

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Filarial diseases

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Mycetoma

Addressing the most neglected diseases through an open research model: the discovery of fenarimols as novel drug candidates for eumycetoma by Lim W, Melse Y, Konings M, Phat Duong H, Eadie K, Laleu B, Perry B, Todd M, Ioset J-R, and van de Sande W. *PLOS Neglected Tropical Diseases*, April 2018

HIV

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HCV

Treatment advocate tactics to expand access to antiviral therapy for HIV and viral hepatitis C in low- to high-income settings: making sure no one is left behind by Grillon C, Krishtel PR, Mellouk O, Basenko A, Freeman J, Mendão L, Andrieux-Meyer I, and Morin S. *Journal of the International AIDS Society*, April 2018

GARDP:

Unavailability of old antibiotics threatens effective treatment for common bacterial infections by Tängdén T, Pulcini C, Aagard H, Balasegaram M, Levy Hara G, Nathwani D, Sharland M, Theuretzbacher U, Cars O. *The Lancet Infectious Diseases*, March 2018

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A WORD OF THANKS

DND*i* has now delivered eight new treatments for neglected patients and aims to deliver another eight to ten in the next five years, for a total of 16-18 new treatments by 2023. DND*i* is deeply grateful for the support of all its donors, and for their commitment and collaboration since 2003. All contributions large and small have contributed toward the advancement of DND*i*'s mission and goals. Listed below are supporters who have given a cumulative contribution of at least USD or EUR 10,000 since 2003.

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- UK aid, UK**
- Unitaid
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Best science for the most neglected

The Drugs for Neglected Diseases *initiative* (DND*i*) is a collaborative, patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for the millions of people across the world affected by neglected diseases, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, filarial infections, paediatric HIV, mycetoma, and hepatitis C.

The Global Antibiotic Research & Development Partnership (GARDP) is a joint initiative of the World Health Organization and DND*i* launched in 2016. It became a fully operational, independent entity in 2019.

DND*i*'s primary objective

Establish a robust R&D portfolio of new drug candidates that addresses patients' treatment needs, deliver 16 to 18 new treatments by 2023 for targeted neglected diseases, and ensure equitable access to these treatments.

In doing this, DND*i* has two further objectives

1. Use and strengthen capacities in disease-endemic countries via project implementation;
2. Raise awareness of the need to develop new drugs for neglected diseases, and advocate for increased public responsibility.

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