New drugs for neglected diseases
New hope for forgotten patients
Developing Drugs for Neglected Patients

DNDi Mission
To develop new drugs, or new formulations of existing drugs, for patients suffering from the most neglected communicable diseases. Acting in the public interest, DNDi bridges existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other partners.

Origins
When the Nobel Peace Prize was awarded to Doctors Without Borders/Médecins Sans Frontières (MSF) in 1999, the organization used a portion of the prize money to create the Drugs for Neglected Diseases Working Group. This group proposed an alternative model for developing new drugs for the most neglected patients, which led to the creation and launch of DNDi in 2003.

DNDi’s Founding Partners
• Doctors Without Borders/Médecins Sans Frontières (MSF)
• Indian Council of Medical Research, India
• Kenya Medical Research Institute, Kenya
• Ministry of Health, Malaysia
• Oswaldo Cruz Foundation, Brazil
• Institut Pasteur, France
• World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) (permanent observer)

Millions of Patients Suffering and Dying Prematurely
Right now, millions of people across the globe are suffering from deadly neglected diseases we hear very little about: sleeping sickness, Chagas disease, and leishmaniasis. Millions of children are living with HIV/AIDS, with a quarter million dying every year. And little-known but debilitating diseases caused by parasitic worms called filaria ruin the lives of many more.

They live in remote villages in South Sudan, the Democratic Republic of Congo, Mexico, and Bolivia; or in crowded shanty towns in India, Brazil, Uganda, and Kenya.

They live in some of the world’s poorest communities, suffering from the least-noticed diseases. They are children like William, a young Sudanese refugee living in the Democratic Republic of Congo, who died because the treatment he received for sleeping sickness was toxic and ultimately as deadly as the parasite it was supposed to kill.

Too many people are living pain-filled lives or dying premature deaths—because they are poor and do not represent a lucrative “market” for the pharmaceutical industry.

This is why DNDi exists.
Drugs for Neglected Patients

The Forgotten Billion: More than 1 billion people—one sixth of the world’s population—are currently infected with one or more neglected tropical diseases (NTDs). Millions more die of malaria. And every year, a quarter million children die of HIV/AIDS.

How DNDi Works

It can be common in the field of medical research for a biologist in the United States, a drug developer in India, and a doctor in Kenya to spend years working on the same neglected disease—with little or no knowledge of each other’s work. By creating innovative partnerships among experts across the globe, and facilitating open exchange of scientific knowledge, DNDi is changing the face of drug development for the world’s poorest people.

Based on patient needs, DNDi acts as a “conductor of a virtual orchestra,” bringing together public research institutions, pharmaceutical and biotechnology companies, universities, non-governmental organizations, other not-for-profit product development partnerships, and governments to carry out highly focused neglected-disease drug development.

DNDi’s Target Diseases:

• Human African trypanosomiasis (sleeping sickness)
• American trypanosomiasis (Chagas disease)
• Leishmaniasis: visceral leishmaniasis (kala azar) and cutaneous leishmaniasis
• Malaria
• Filaria
• Pediatric HIV/AIDS

DNDi’s Achievements

Since 2003, DNDi has developed and delivered six new treatments for neglected patients:

• ASAQ for malaria: Provides simplified dosing and is more affordable than earlier drugs, with over 150 million treatments distributed for sub-Saharan Africa.
• ASMQ for malaria: Provides convenient dosing, including for children, and is low cost, for resistant cases in southeast Asia and Latin America. Registered in Brazil and South Asia.
• NECT for sleeping sickness: The first new therapy for sleeping sickness in 25 years simplifies treatment in the field and has replaced the toxic drug melarsoprol (an arsenic derivative), with over 10,000 treatments distributed in Central Africa.
• SSG&PM combination therapy for visceral leishmaniasis in Africa: Reduces treatment duration by nearly half, making it far less burdensome for patients and clinicians, and decreases total cost.
• A set of combination treatments for visceral leishmaniasis in Asia: Decreases treatment duration and treatment costs, for use in India, Bangladesh, and Nepal.
• Pediatric dosage form of benznidazole for Chagas disease: This 12.5-mg tablet allows more accurate dosing in infants and young children under two years old, compared with the standard adult tablet. Registered in Brazil.

DNDi’s Goals

• Develop 5–7 new treatments, in addition to the 6 already developed, for a total of 11–13 new treatments by 2018
• Create a robust pipeline of drug candidates that further address patient needs
• Strengthen research capacity in countries where neglected patients live
• Advocate for greater international attention to R&D for neglected diseases and patients
• Ensure patient access to new medicines
They are both virtually invisible to the pharmaceutical industry because the current system for researching and developing medicines and other health tools prioritizes commercial rewards and “return on investment” for shareholders over global public health needs.

When DNDi was formed, only about 10% of the world’s spending on health research went towards diseases affecting 90% of the world’s population, the vast majority of whom live in the developing world. This “10/90 gap” meant that very few drugs were being developed for diseases that predominantly or exclusively affected poor people in low- and middle-income countries.

Although there have been several positive trends in the past decade, with new players entering the neglected-disease R&D field, it has not been nearly enough. The continued lack of safe, effective, affordable, and field-adapted medicines is partly why deadly neglected diseases that are preventable and treatable continue to kill millions of the world’s poorest people every year.

By bringing together international experts from across the globe, DNDi is demonstrating that innovative, patient-centered, non-profit approaches to drug development can deliver new and adapted medicines for those most in need.

Your support can help DNDi develop new medicines to improve the lives of millions of people suffering from diseases in some of the world’s most impoverished communities.


**Tropical diseases: 18 new drugs (including 8 for malaria)**

**Tuberculosis: 3 new drugs**

1975 - 2004

<table>
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<th>Period</th>
<th>Tropical diseases</th>
<th>Tuberculosis</th>
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<td>1975 - 2004</td>
<td>18 new drugs</td>
<td>3 new drugs</td>
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98.7% of new drugs were for other diseases, 1.3% were for neglected diseases.
Killed by the Drug Meant to Treat Him

You do not feel very proud to be a doctor when the only drug you can give your patients is basically a poison. But we had no other choice because we were facing a neglected disease that is fatal if untreated. As physicians, we found this unacceptable, and our frustration led to the formation of DNDi.”

Dr. Bernard Pécoul,
Executive Director, DNDi

William was just 13 when he came down with fever, erratic sleep patterns, and crippling headaches—classic symptoms of sleeping sickness.

As a refugee from Sudan living in the Democratic Republic of Congo, William had probably been infected while collecting water or bathing in a nearby river. That is where the tsetse fly, which transmits the trypanosome parasite, lives, and this is how sleeping sickness spreads in many communities in sub-Saharan Africa.

In its late stage, sleeping sickness affects the brain, causing severe neurological disturbances. As the disease progresses, patients slip into a coma. Then, without treatment, they inevitably die.

William’s family had no choice but to accept the only treatment available at the time—melarsoprol—a drug derived from arsenic that is so toxic it kills one in 20 patients. It has been known to melt plastic syringes and has been called “fire in the veins.” After just one injection, William died.

Tragic stories like William’s were commonplace in sub-Saharan Africa just 10 years ago. And the plight of patients like William motivated Doctors Without Borders and concerned scientists to create DNDi in 2003.

DNDi, working together with Doctors Without Borders, the World Health Organization, and other partners, developed nifurtimox-eflornithine combination therapy, or NECT—a safe and effective combination therapy for late-stage sleeping sickness. The first new treatment for sleeping sickness in 25 years, NECT has reduced the complexity, duration, and cost of treatment. It has also helped virtually eliminate the use of melarsoprol and is in widespread use in sub-Saharan Africa today.

It came too late for William. But thanks to this new treatment, thousands of children like him will no longer die because nobody created better medicines for them.

To meet the needs of patients in the long term and potentially eliminate sleeping sickness, a bigger scientific breakthrough is still needed. Although NECT was an improvement, it still only treats the late stage of the disease and requires intravenous (IV) infusions and at least a week of hospitalization, which are often difficult where sleeping sickness is prevalent.

DNDi is working on developing a simple, easy-to-take, oral pill, one that is safe and effective against both the early and late stages of the disease, which would do away with the need to perform painful lumbar punctures on patients to determine disease stage.

DNDi has two promising oral drug candidates in clinical trials, fexinidazole and oxaborole. With continued support, DNDi hopes to successfully develop and deliver at least one of these drugs to patients.

“In its short existence, DNDi has already shown remarkable capabilities in executing drug discovery and development programs. The opportunity to relieve the suffering of neglected patient populations is immense.”

Dr. Bennett Shapiro,
Chair, DNDi North America Board of Directors
Former Executive Vice President, Merck

DNDi North America
**DNDi Target Diseases:**

### Sleeping Sickness
**Human African Trypanosomiasis (HAT)**
*Transmitted by tsetse flies*

- 60 million people at risk in sub-Saharan Africa
- Kills 100% of victims if left untreated
- Can cause severe mental disturbances and sleep disruptions, leading ultimately to paralysis, coma, and death
- Poverty and war contribute to disease “hot spots”

**LIMITATIONS OF CURRENT TREATMENTS**
- For many years, the only treatment available was melarsoprol—an arsenic-based drug so toxic it kills one in 20 patients and so painful it was nicknamed “fire in the veins”
- Current treatments still require hospitalization, which is difficult in the field
- Painful spinal taps are required to determine stage of disease

**URGENT PATIENT NEEDS**
- Oral pill taken just once a day, for less than a week
- Treatment that cures both stages of the disease, to eliminate the need to do painful spinal taps

### Chagas Disease
**American Trypanosomiasis**
*Transmitted primarily by “kissing bugs”*

- Estimated 8 million cases primarily in Latin America, with an estimated 300,000 in the US
- Kills 12,000 people each year
- Attacks the heart or digestive system of one-third of patients, threatening their lives
- Can be passed from mother to child during pregnancy
- Leading parasitic killer in North and South America, causing more deaths than malaria

**LIMITATIONS OF CURRENT TREATMENTS**
- The only two drugs currently available (benznidazole, nifurtimox) were developed almost 40 years ago, neither specifically for Chagas disease
- Side effects (severe rash, nausea, vomiting, stomach pain, anorexia) often force patients to stop treatment
- Low effectiveness (10-20% cure) in late-stage disease
- Long periods of treatment (30-90 days)
- Cannot be taken by pregnant women

**URGENT PATIENT NEEDS**
- Safe, effective drug adapted for use in the field and ideally treats both stages of the disease
- A simple test to show the patient has been cured

### Visceral Leishmaniasis (VL)
**Kala Azar**
*Transmitted by sandflies*

- Estimated 500,000 cases in 70 countries in Africa, Asia, Latin America, and Middle East
- Kills 50,000 people each year, and is 100% fatal if left untreated
- Causes fever, swollen organs, severe weight loss, and anemia
- HIV-VL co-infection is a growing concern

**LIMITATIONS OF CURRENT TREATMENTS**
- Pentavalent antimonials: toxic, increasing drug resistance, long treatment duration, requires hospitalization
- Amphotericin B: toxic, long treatment duration, requires hospitalization
- Paromomycin: registered in India only, requires 3 weeks of injections
- Miltefosine: potentially causes cancer, thus cannot be given to pregnant women; expensive
- Liposomal amphotericin B (AmBisome®): expensive, requires injection

**URGENT PATIENT NEEDS**
- Safe, effective, low-cost daily oral pill, eliminating injections
- Treatment duration of ideally less than 10 days
- Drug with long shelf life that can be stored in hot, tropical climates

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**DNDi Achievements**
- **NECT** (nifurtimox-eflornithine combination therapy), launched in 2009
- **DNDi** is currently developing two new oral drug candidates: fexinidazole and oxaborole.

**DNDi Achievements**
- **SSG&PM** (sodium stibogluconate and paromomycin), launched in 2010, for Africa
- A set of combination therapies, launched in 2011, for Asia
- **DNDi** has three clinical development programs for improving current treatments in East Asia, East Africa, and Latin America, and three new-drug projects in the preclinical stage.
Deadly and Debilitating

Malaria
*Plasmodium falciparum*
Transmitted by mosquitoes

- More than 200 million cases worldwide
- Kills at least one child every minute
- Estimated 655,000 to 1.2 million deaths each year, mainly children

Filaria
Specific Helminth Infections
Transmitted by blackflies, mosquitoes, mango flies, and deer flies

- Onchocerciasis (River Blindness) and Lymphatic Filariasis (Elephantiasis), co-infected with Loiasis (Loa loa; African Eye Worm)
- Filaria is a term covering three parasitic-worm diseases: river blindness, elephantiasis, and African eye worm
- Estimated 168 million people infected worldwide, mainly children
- Over 1 million people blinded or visually impaired

- 25 million men have genital disease, and 15 million, mostly women, have massive leg swelling
- Severely disabling and disfiguring, leading to social stigmatization, isolation, and loss of work and educational productivity

LIMITATIONS OF CURRENT TREATMENTS

- In co-infections of all three diseases, the current drug ivermectin can cause brain damage or even death – over 14 million people are at risk
- Current treatments primarily kill young worms but not adult worms, so repeated annual treatments are required

URGENT PATIENT NEEDS

- Safe, effective drug that targets adult worms
- Drug that can help reduce the need for repeated treatments

DNDi’s Priorities

DNDi launched a new program to develop a safe, effective macrofilaricide [drug capable of killing adult worms]. If successful, this drug will help tremendously in disease control or elimination.

DNDi Achievements

- ASAQ (artesunate and amodiaquine), launched in 2007, for sub-Saharan Africa
- ASMQ (artesunate and mefloquine), launched in 2008, mainly for resistant malaria in Southeast Asia and Latin America

DNDi is handing over implementation of its malaria projects to partners to ensure continued patient access to the drugs. Handover to be completed in 2014.

Pediatric HIV/AIDS

- 3.4 million children (<15 years old) are living with HIV/AIDS
- 1,000 children are born or newly infected with HIV every day, over 90% in sub-Saharan Africa
- 700 children die from AIDS-related complications each day

- Without treatment, 80% of children infected will die before the age of 5
- Less than a quarter of children in need of antiretroviral treatment are receiving it

LIMITATIONS OF CURRENT TREATMENTS

- Current formulations, typically syrups, taste terrible for children
- Impractical for caregivers because they require refrigeration, many complicated liquid preparations, and must be adjusted according to the child’s weight
- Undesirable interactions with drugs for tuberculosis (TB), the most common co-infection with HIV
- Safety and correct dosing of key antiretrovirals have not been established for young children

URGENT PATIENT NEEDS

- Infants and young children under 3 years of age
- Child-adapted antiretroviral formulations, easily dissolvable or mixable, and well tolerated in terms of taste
- Stable in hot tropical climates, compatible with TB drugs, and affordable

DNDi’s Priorities

In 2011, DNDi launched a new program to develop antiretroviral drug formulations and combinations designed specifically for infants and young children.
DNDi’s partners screen thousands of chemical compounds for activity against neglected-disease parasites. The strongest “hits” eventually move to preclinical testing.

Drug compounds from discovery research are tested in the laboratory and in animals to determine if they are potentially safe enough to be tested in humans.

- **Phase I clinical trials:** First-in-human studies
- **Phase II clinical trials:** Efficacy, safety, and dosing studies
- **Phase III clinical trials:** Large-scale efficacy and safety studies

If the clinical trials are successful, DNDi will work with its partners to get the new medicine approved, registered, and into the hands of patients who need it most.

**Key US partners:**
- Pace University, New York
- Sandler Center, University of California, San Francisco
- Anacor Pharmaceuticals, Palo Alto, CA
- SCYNEXIS, Research Triangle Park, NC

The Story of Oxaborole SCYX-7158

In the pipeline: How DNDi is developing a new drug for patients with sleeping sickness

**2007 – 2009**
A total of 730 compounds from a novel class of chemicals called oxaboroles were screened by DNDi’s US partners and tested for activity against the sleeping sickness parasite in the laboratory. The oxaborole compound SCYX-7158 was identified and put forth as a preclinical drug candidate at the end of 2009.

**2010 – 2011**
Oxaborole was studied in lab animals and shown to be effective against both early- and late-stage sleeping sickness, as well as safe enough to be tested in humans. The preclinical findings were published in the open access journal *Public Library of Science (PLoS) Neglected Tropical Diseases* in 2011.

**2012 – 2016**
A Phase I clinical trial of oxaborole in healthy adults started in early 2012 in Paris, France. This first-in-human, randomized controlled trial of oxaborole will test the drug candidate’s safety, tolerability, and drug levels in the body. If successful, Phase II/III trials will study the effectiveness and safety of oxaborole in patients with sleeping sickness in the field.
new drugs. DNDi strives to use manufacturers in developing countries whenever possible.

**Phase IV Clinical Studies:** After market introduction, DNDi and its partners conduct Phase IV studies of new drugs in larger and more diverse populations to gather further safety and efficacy data.

DNDi strives to take a more open approach to boosting innovation for new drug discovery and development for neglected diseases, including the public sharing of scientific knowledge and royalty-free, non-exclusive licensing agreements with our pharmaceutical partners. With this “open innovation” strategy in mind, the six new treatments DNDi has developed are non-patented, affordable, and available as public goods.

**AVAILABLE TO PATIENTS**

DNDi strives to use manufacturers in developing countries whenever possible.

**AVAILABLE TO PATIENTS**

- **Chagas Clinical Research Platform (CCRP)**
  - A network of health agencies and scientists in the Americas and around the world that aims to strengthen capacity, expand community participation, and improve evaluation and delivery of new treatments across the region.

- **Leishmaniasis East Africa Platform (LEAP)**
  - A research capacity-strengthening network of health agencies and scientists from the four African countries most affected by visceral leishmaniasis (Ethiopia, Kenya, Sudan, Uganda) as well as international experts. The LEAP platform has established seven trial sites and trained principle investigators, lab technicians, and monitors.

- **HAT Platform**
  - A research capacity-strengthening network of clinicians, national control program representatives, and scientists from the African countries most affected by sleeping sickness (Angola, Central African Republic, Chad, Democratic Republic of the Congo, Republic of the Congo, Sudan, South Sudan, Uganda) as well as international institutions.
Improving the Lives of Millions Suffering from Treatable Diseases Requires Significant Funding. We Need Your Help.

DNDi has made significant progress toward providing safe, affordable, effective and adapted medicines for the world’s most neglected patients. Our initial goal was to develop six to eight new treatments by 2014. By 2011, we had successfully delivered six new life-saving medicines, two years ahead of schedule.

With the largest-ever portfolio of promising drugs for our target diseases, DNDi’s drug-development model is fully capable of delivering 5 to 7 additional new treatments by 2018. But our success relies on the generosity of donors like you.

Please consider supporting DNDi’s work today.

Your contribution will directly fund the development of new medicines, as well as help bring the six treatments already developed by DNDi to millions more patients.

Your donation is urgently needed to save lives. We can—and must—turn the tide against these diseases that cause great suffering and death.

What Your Support Provides

Every year, millions of the world’s poorest and most marginalized people die from neglected diseases like sleeping sickness, Chagas disease, leishmaniasis, malaria, and pediatric HIV. DNDi is working to change this.

With the largest-ever portfolio of promising drugs for our target diseases, DNDi’s drug-development model is fully capable of delivering 5 to 7 additional new treatments by 2018. But our success relies on the generosity of donors like you.

Please consider supporting DNDi’s work today.

→ A treatment for children with Chagas disease.
→ A simple pill for the treatment of sleeping sickness.
→ An effective treatment for children with HIV/AIDS.

All this and more is possible—with your help.

Generous contributions from individuals like you help to:

• Save the lives of millions of patients suffering from neglected diseases now, by ensuring access to the new treatments already developed by DNDi and our partners

• Create improved versions of existing drugs, including formulations or dosage forms adapted for children

• Discover and develop novel drug candidates for sleeping sickness, Chagas disease, leishmaniasis, and parasitic worm infections

• Strengthen research capacity in neglected disease-endemic countries by training scientists and health workers and equipping labs and clinics

• Forge innovative partnerships to share knowledge, avoid duplication, and speed up the R&D process for the benefit of patients

• Advocate for increased attention and resources for R&D for neglected diseases and patients

Donors

DNDi is supported by a wide range of public and private funders including Doctors Without Borders as a founding partner; governments including the UK, the Netherlands, Germany, France, Switzerland, the US (National Institutes of Health), and Spain; private philanthropic organizations including the Bill & Melinda Gates Foundation, Wellcome Trust, other foundations, and individual private donors.

To ensure the greatest possible independence, DNDi seeks to diversify its funding sources, maintain a balance of public and private support, and ensure that no single donor contributes more than 25% of DNDi’s overall budget.
WAYS TO DONATE

Every gift to DNDi, large or small, makes a difference. Through careful stewardship, we make sure the funds you have so generously entrusted to us go where they are needed the most.

86% of the money we spend goes directly to programs that create life-saving medicines. You can be confident your donations will be used effectively and efficiently to make a difference.

Donate by Mail
Support DNDi by making your check or money order payable to DNDi North America. If you would like to print a donation form to mail along with your check or credit card information, please visit: www.dndina.org/donate

Mail your gift and any correspondence to:
DNDi North America
40 Wall Street, 24th Floor
New York, NY, 10005

Donate by Phone
Provide your credit card information over the phone or receive gift-related assistance by calling the DNDi North America Development Office at: (646) 616-8682.

Donate Online
Make a secure online donation by visiting our website at: www.dndina.org/donate

GIFTS WITH SPECIAL IMPACT

The Leadership Circle

The Leadership Circle honors philanthropic leaders who have made significant contributions of $10,000 or more to DNDi North America and who have demonstrated a commitment to working with DNDi. Leadership Circle gifts make a major difference in DNDi’s efforts to ensure that the most neglected and forgotten patients in the world’s poorest and most vulnerable communities. DNDi North America will send a notification letter to the party of your choice informing them of this special recognition.

Tribute Gifts

By dedicating a tribute gift, you can honor or remember someone in a meaningful way. Remember a loved one or celebrate a birthday, wedding, graduation, or any special occasion, while making a difference in the lives of neglected patients in the world’s poorest and most vulnerable communities.

Matching Gifts

Many employers sponsor matching gift programs and will match your charitable contribution. The impact of your donation towards our initiatives can be significantly increased with a double or sometimes even a triple match. Provide DNDi North America with your employer information, and we can help you determine the eligibility requirements of your employer’s matching gift program.

Recurring Gifts

When you make a recurring gift on a monthly or quarterly basis, you are demonstrating your loyalty to our important work and guaranteeing the continuation of our life-changing programs.

TAKE ACTION NOW

• Make a financial contribution to DNDi
• Subscribe to our e-News and learn more about our life-changing work
• Host a fundraising or awareness-raising event for DNDi
• Follow us on Facebook, Twitter, and YouTube
To make a tax-deductible contribution, please make check payable to:

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