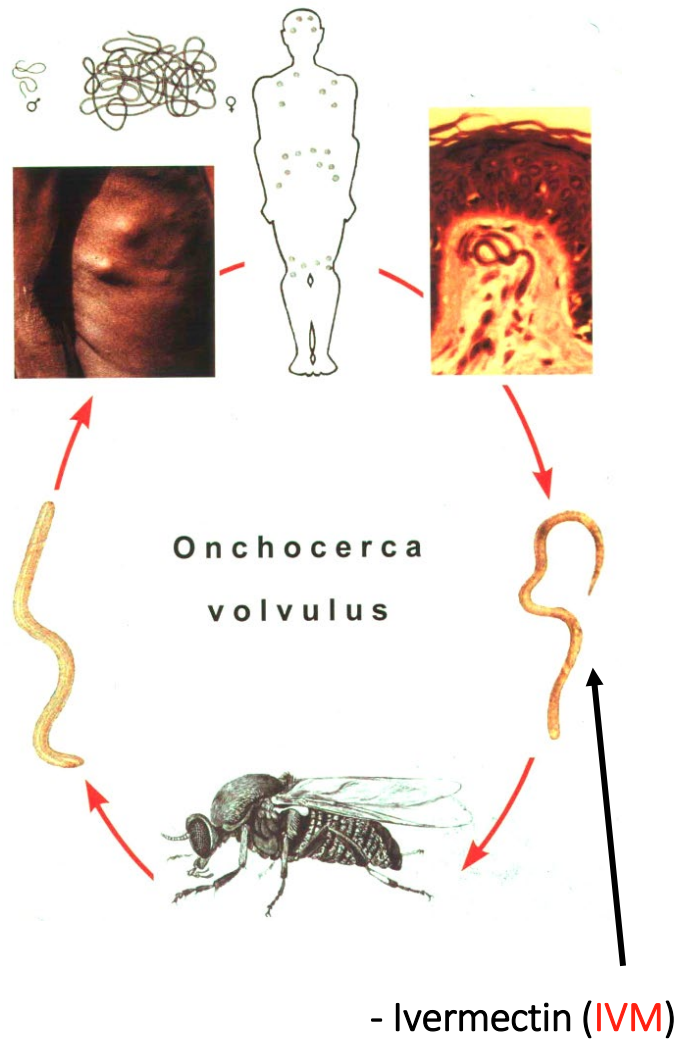

Session 4 - Current research landscape in onchocerciasis

Clinical research in onchocerciasis

Onchocerciasis Research Network and DND/stakeholder event
October 3 - 4, 2018
Kampala, Uganda

Ute Klarmann-Schulz

Institute for Med. Microbiology, Immunology and Parasitology (IMMIP)
German Center for Infection Research (DZIF), partner-site Bonn-Cologne
University Hospital of Bonn
Bonn, Germany



ISRCTN50035143

Death to Onchocerciasis and Lymphatic Filariasis: Comparison of Ivermectin alone with Albendazole (ALB) plus Ivermectin (IVM) in their efficacy against Onchocerciasis

In total 272 Mf-positive participants, with at least one palpable onchocercoma were treated with either:

Annual treatment (0, 12, 24 months):

- 1) IVM 200µg/kg annually
- 2) IVM 200µg/kg plus ALB 800mg annually

Semi-annual treatment (0, 6, 12, 18, 24 months):

- 3) IVM 200µg/kg semi-annually
- 4) IVM 200µg/kg plus ALB 800mg semi-annually.

ISRCTN50035143

Death to Onchocerciasis and Lymphatic Filariasis: Comparison of Ivermectin alone with Albendazole (ALB) plus Ivermectin (IVM) in their efficacy against Onchocerciasis

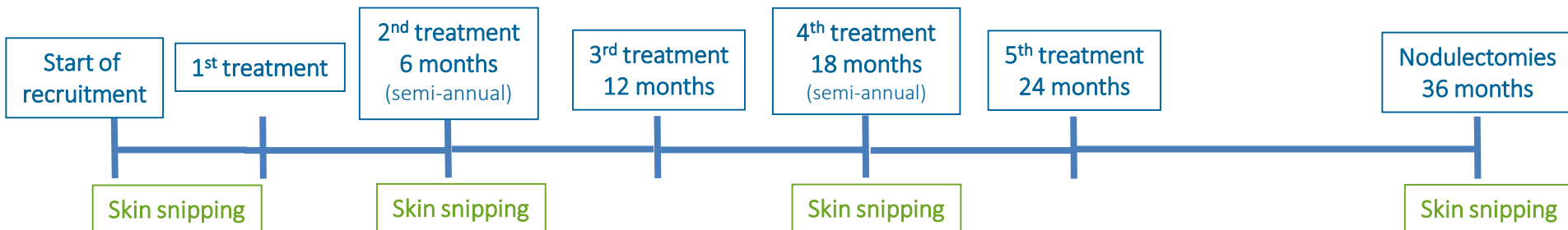
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- 3) IVM 200µg/kg semi-annually
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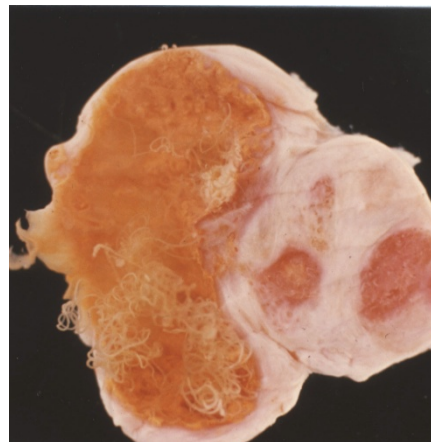
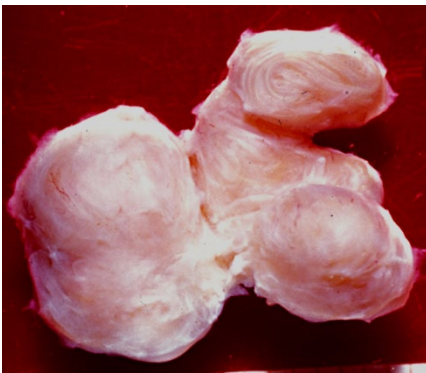
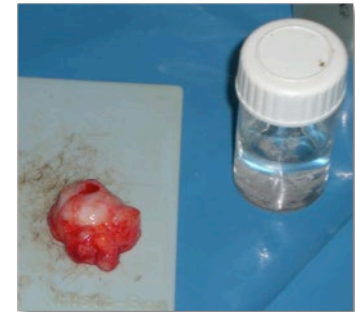
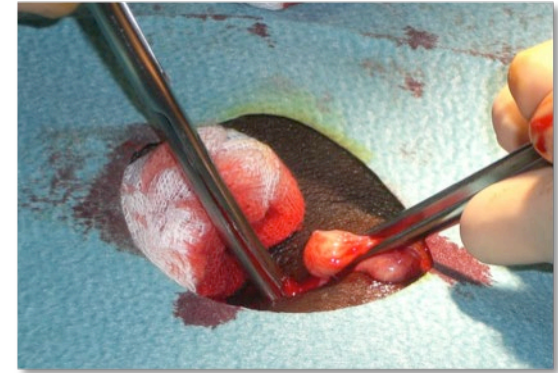


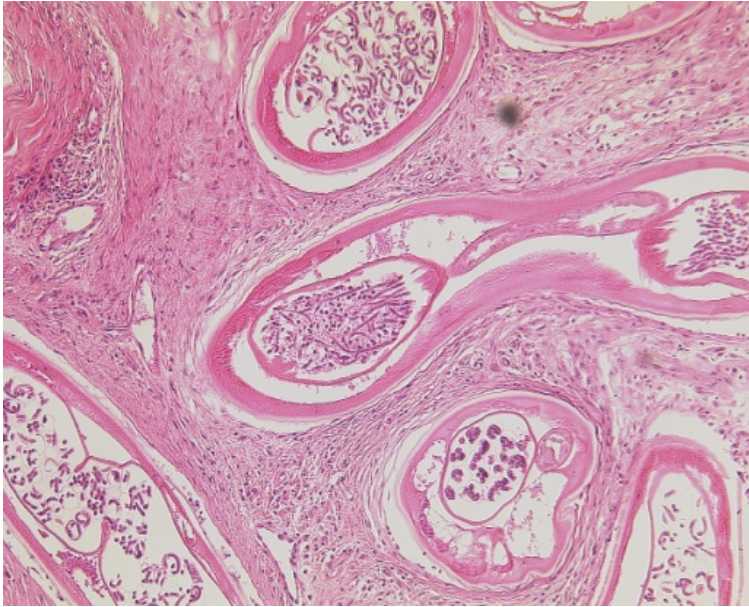


Surgical extirpation of onchocercomata (Nodulectomies)

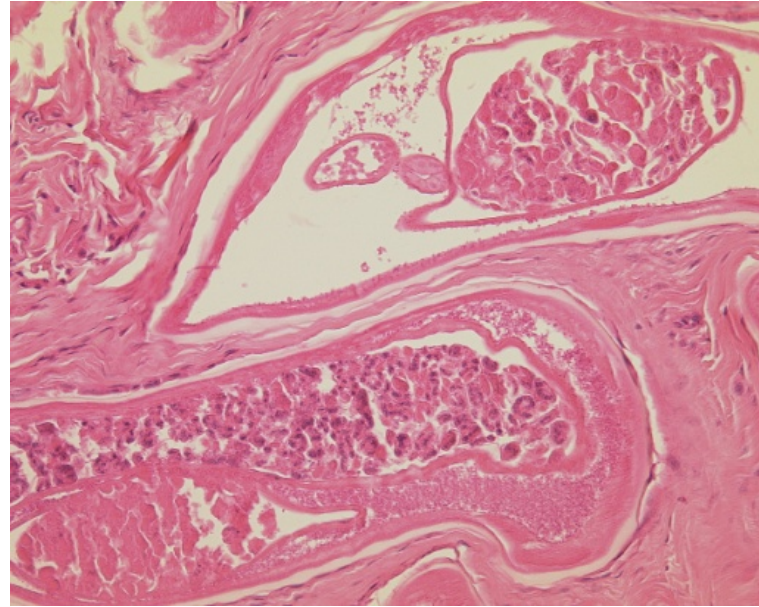


Surgical extirpation of onchocercomata (Nodulectomies)





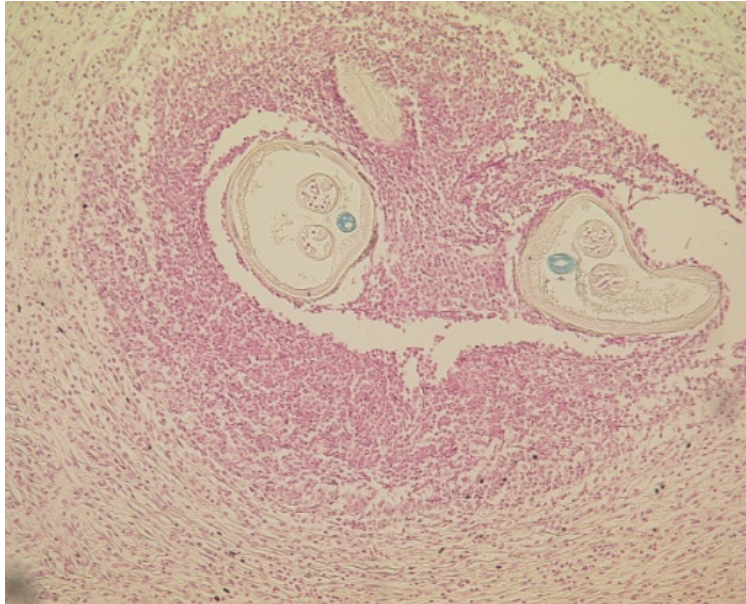
Normal embryogenesis



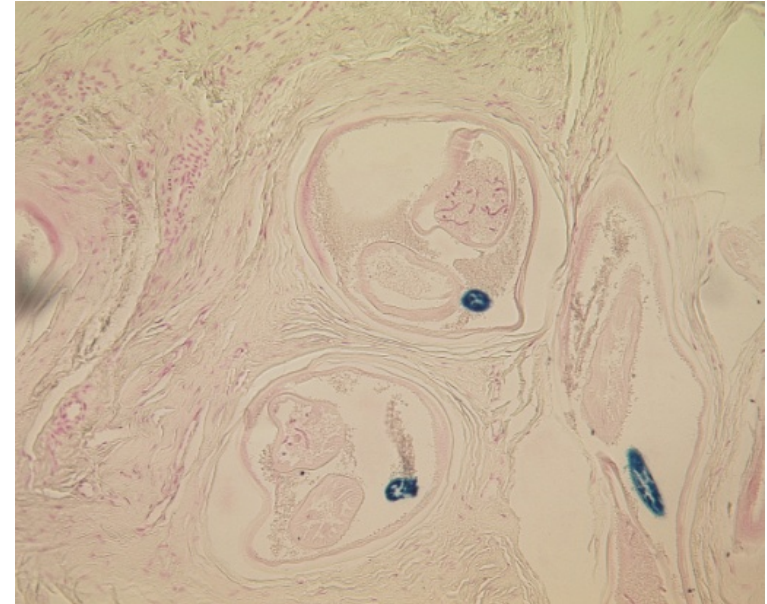
Degenerated embryogenesis

Evaluations

- Nodules: nodule size; number & position of worms
- Worms: size, sex, age, morphology (hypodermis, cuticle), live / dead, sperms
- Female worms: embryogenesis, microfilaria, uterus (embryonic stages)



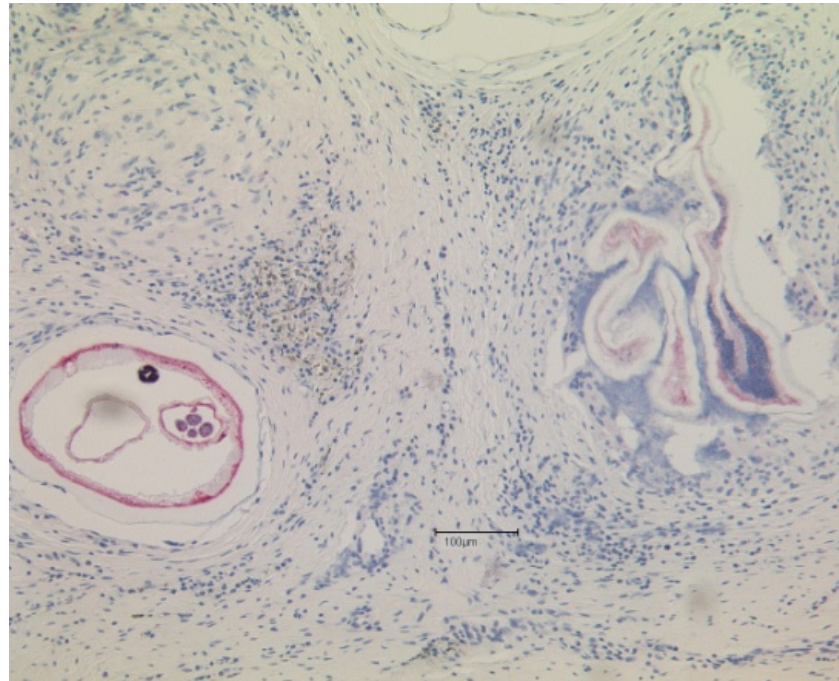
Young worm (weak FE III)



Old worm (strong FE III)

Evaluations

- Worms: age



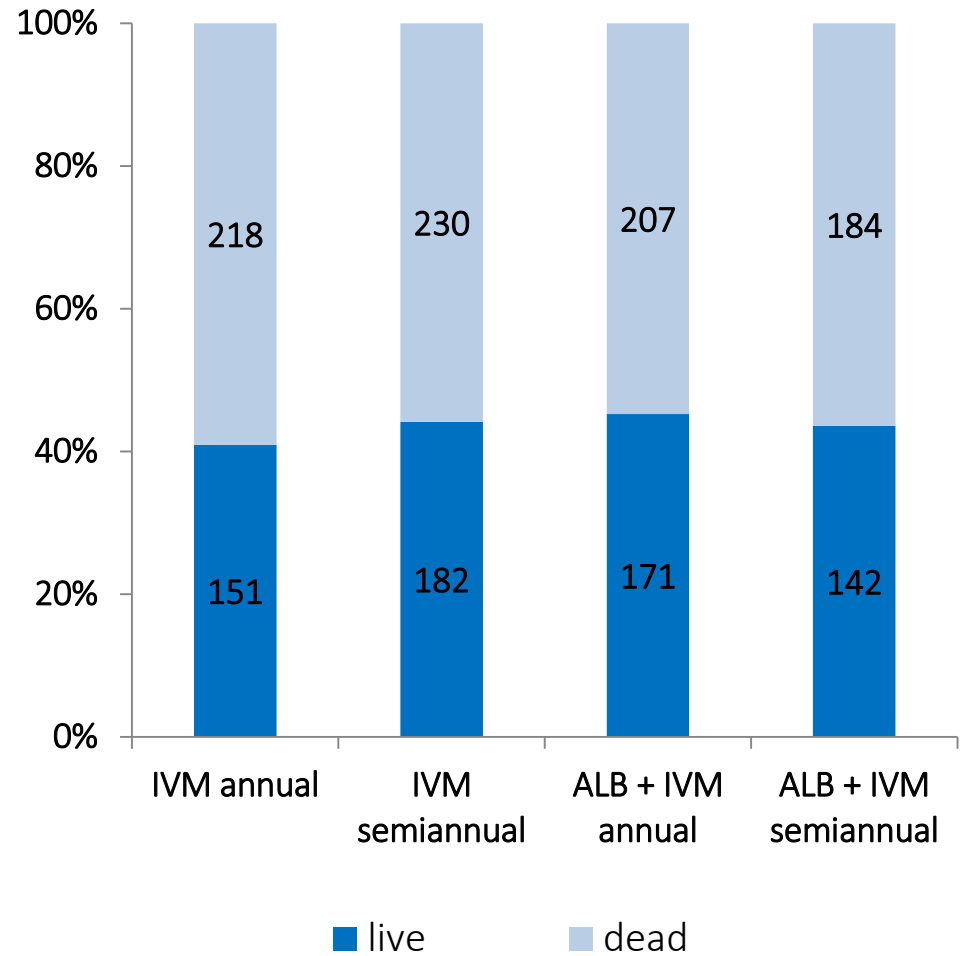
Live worm
(APR positive, left)

Dead worm
(APR negative, right)

Evaluations

- Worms: live / dead
 - Dead worms: calcification, resorption
 - Live worms: morphology, sperms, uterus possible (embryonic stages)

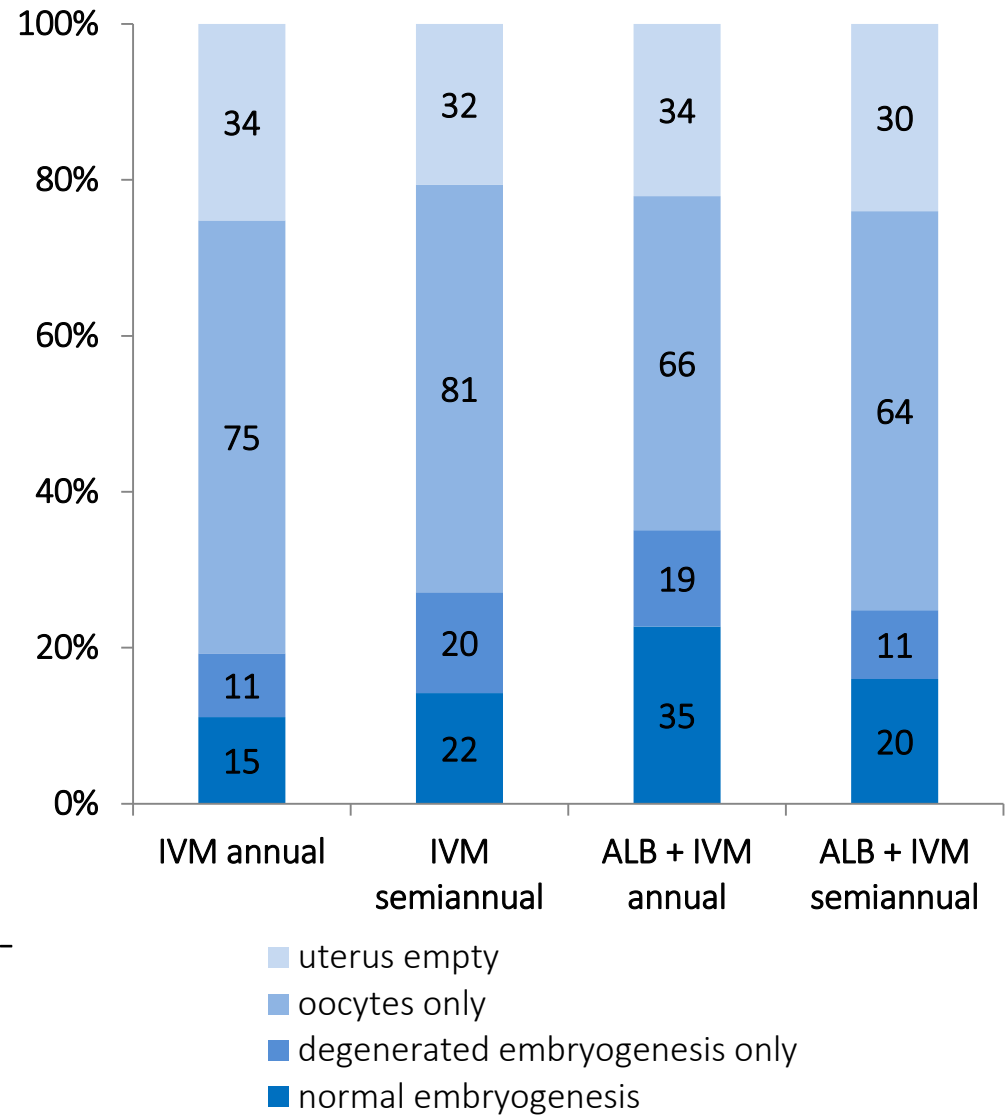
With a range of 55 - 59% the proportion of dead worms did not differ between the 4 groups.

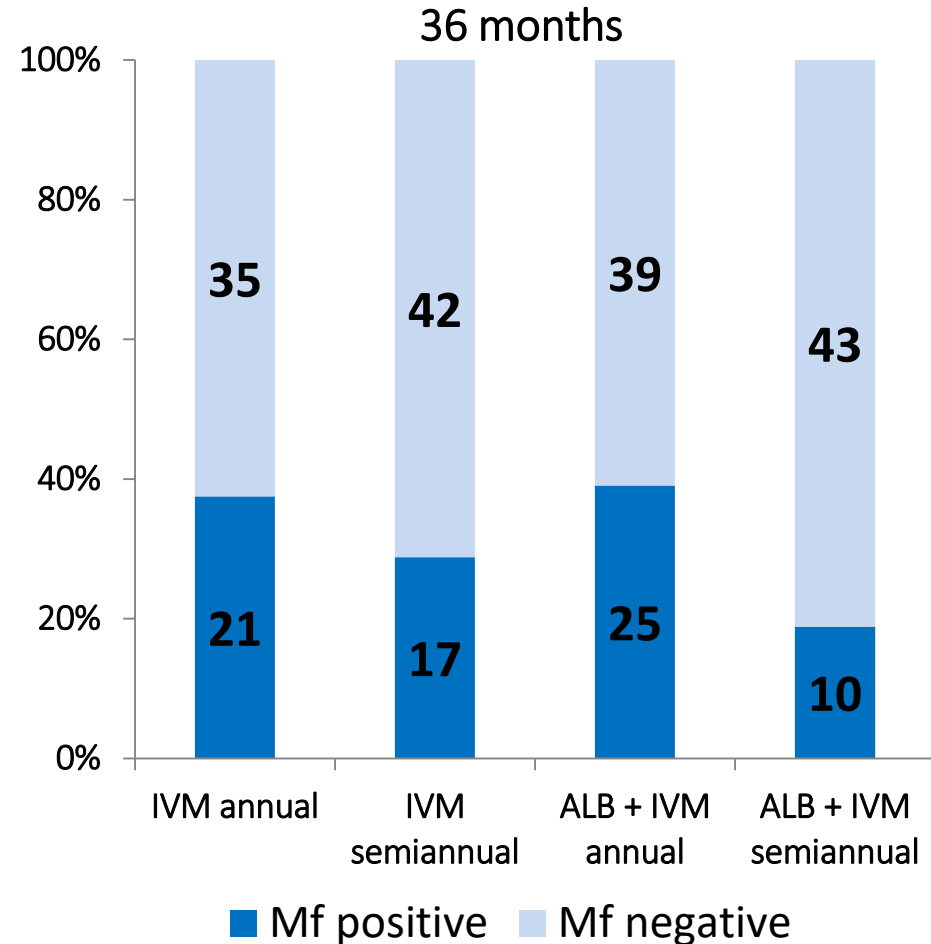
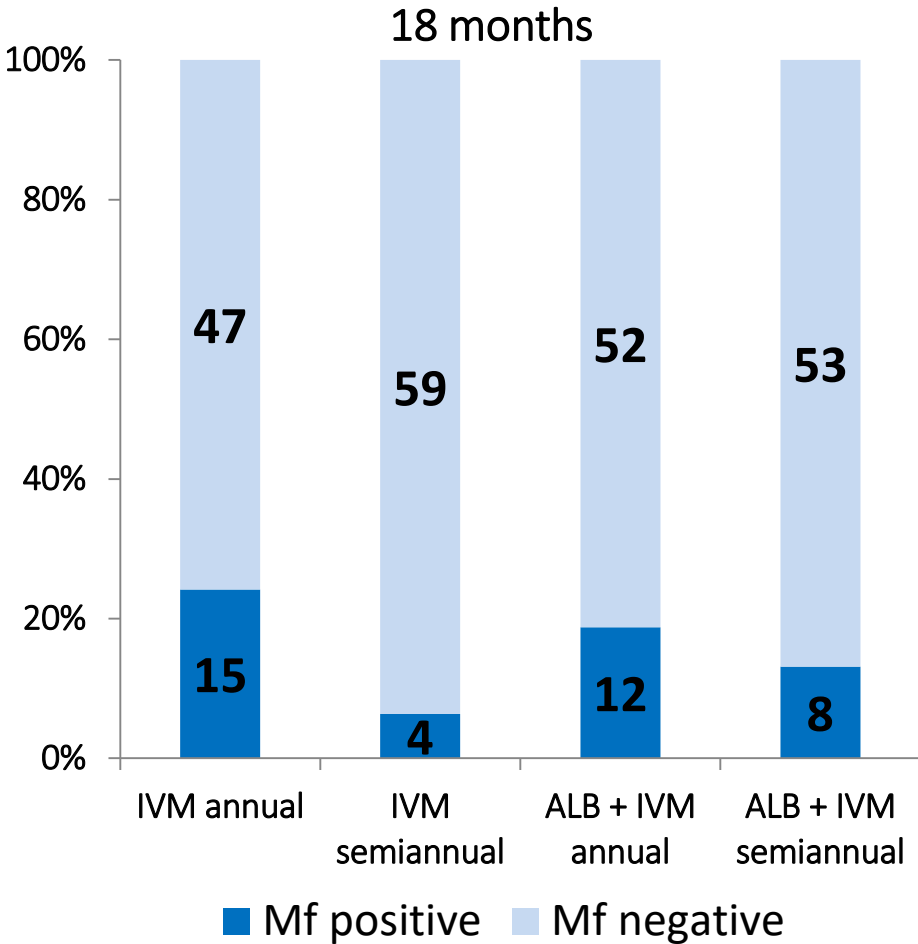


Number of live and dead female worms per treatment group. 4-group comparison $p = 0.9198$ (Proc Genmod, SAS®)



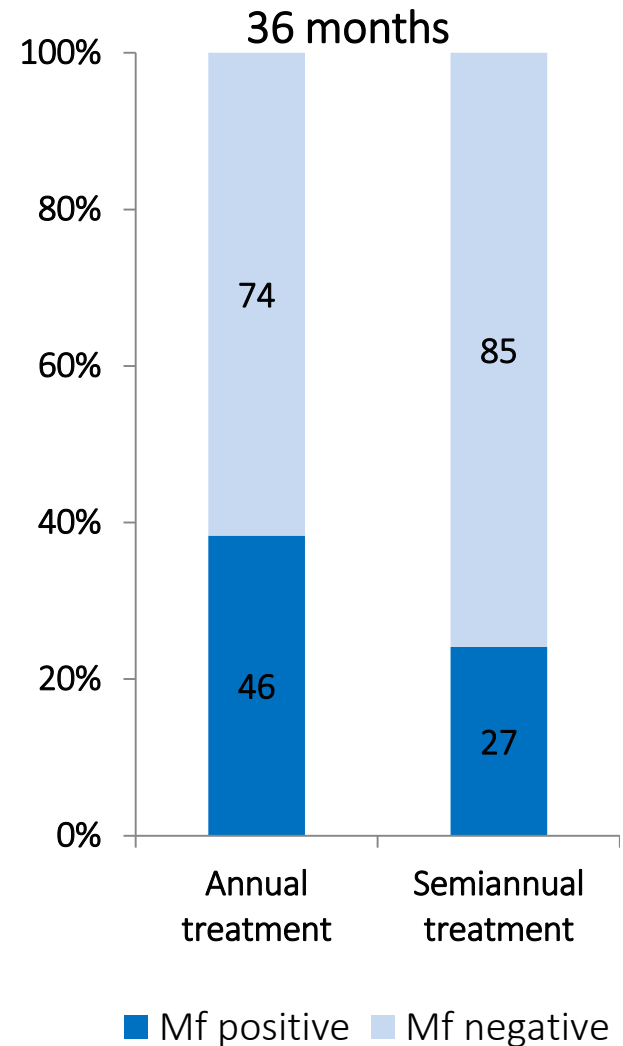
Number of live female worms with normal or degenerated embryogenesis, oocytes only or empty uterus per treatment group. 4-group comparison $p = 0.1229$ (Proc Genmod, SAS®)







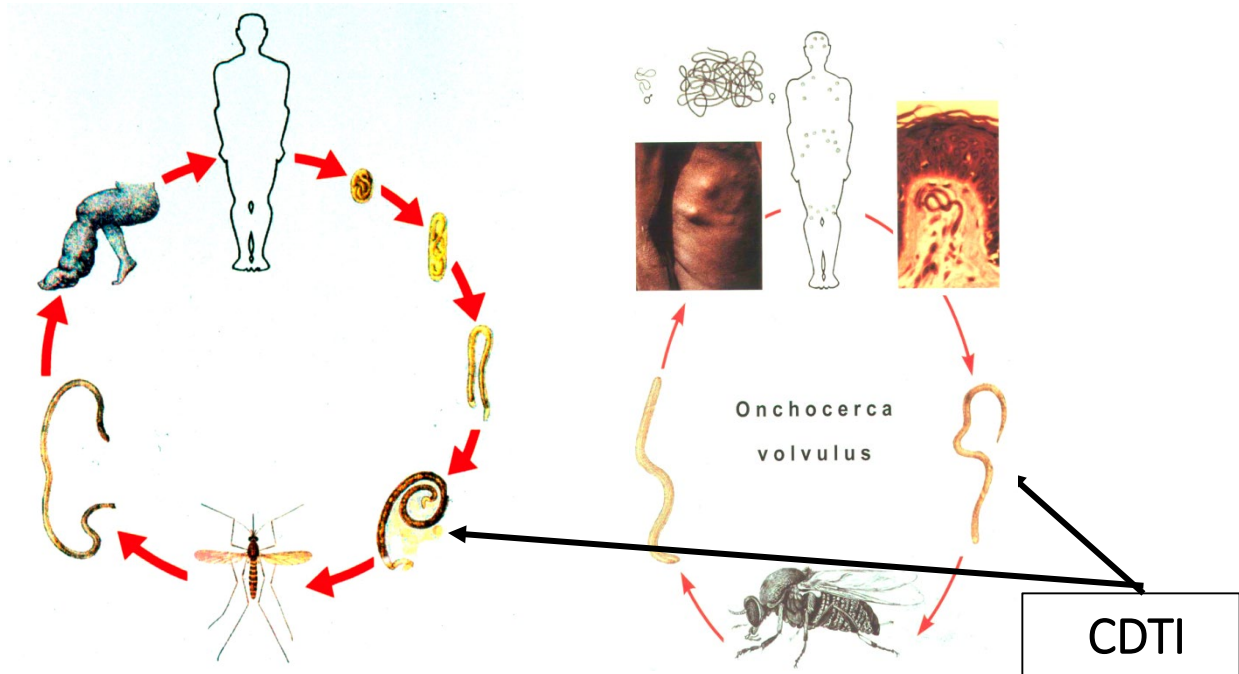
Number of Mf-positive/ Mf-negative participants grouped for annual or semiannual treatment without taking the addition of ALB into account
 $p = 0.024$ (Fisher`s exact test)



Alternative treatment strategies (ATS) are needed where community directed treatment with ivermectin (CDTI) is not sufficient because of:

- low treatment coverage
- areas co-endemic for loiasis
- suboptimal response

(WHO ATS-report 2015)

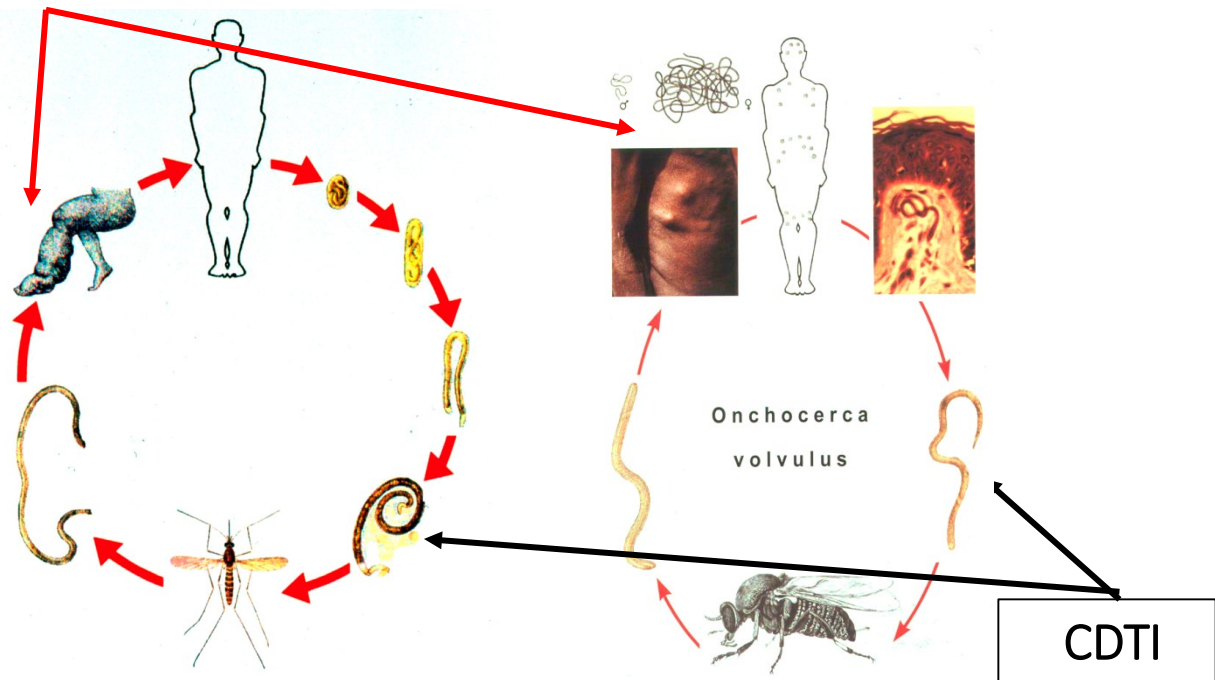


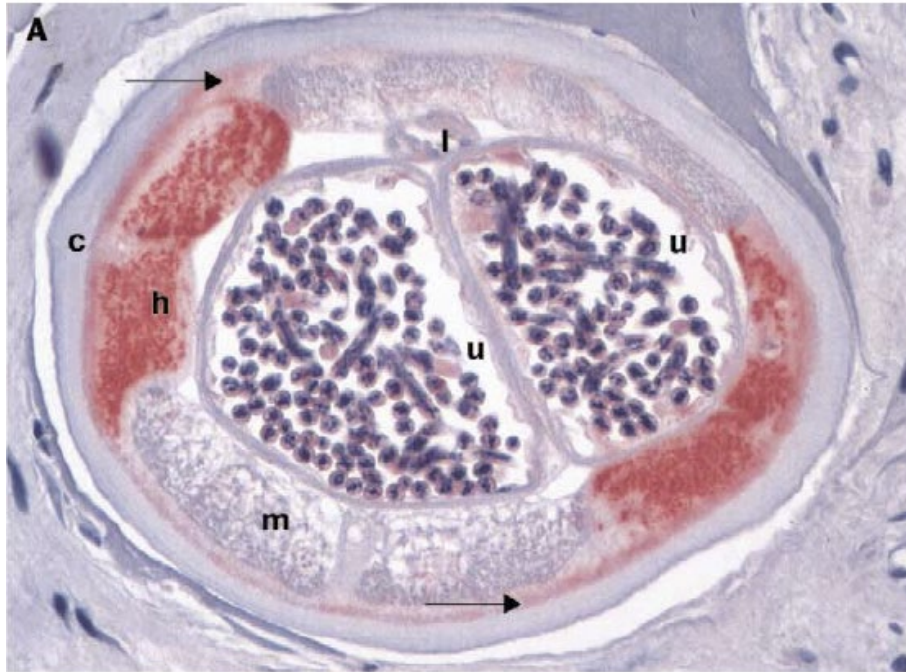
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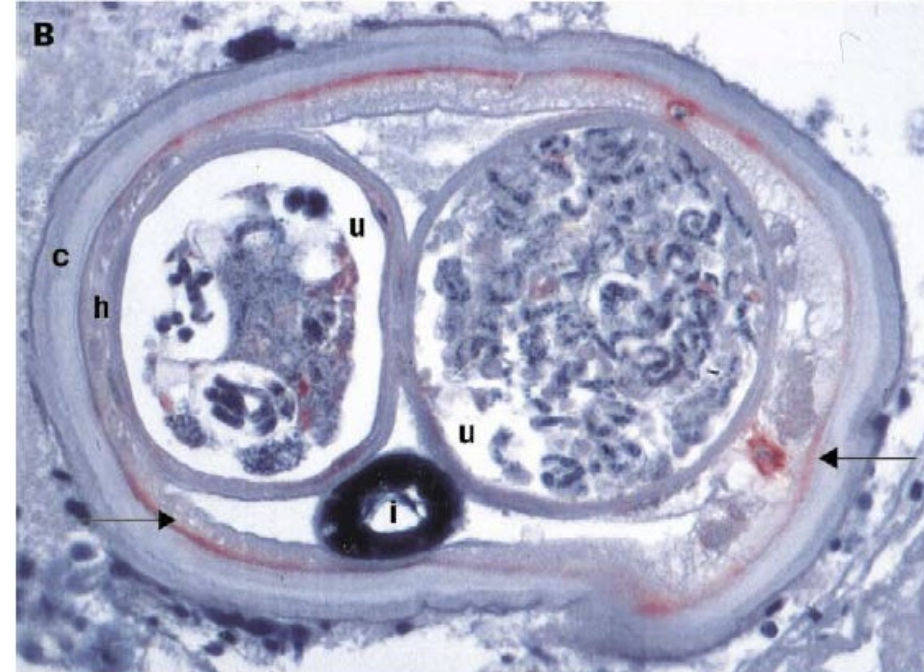
→ drugs with **adulticidal** activity

- Re-purposing of registered drugs
- Optimization of drug candidates
- Identification of novel drugs that target *Wolbachia* or have another mode of action



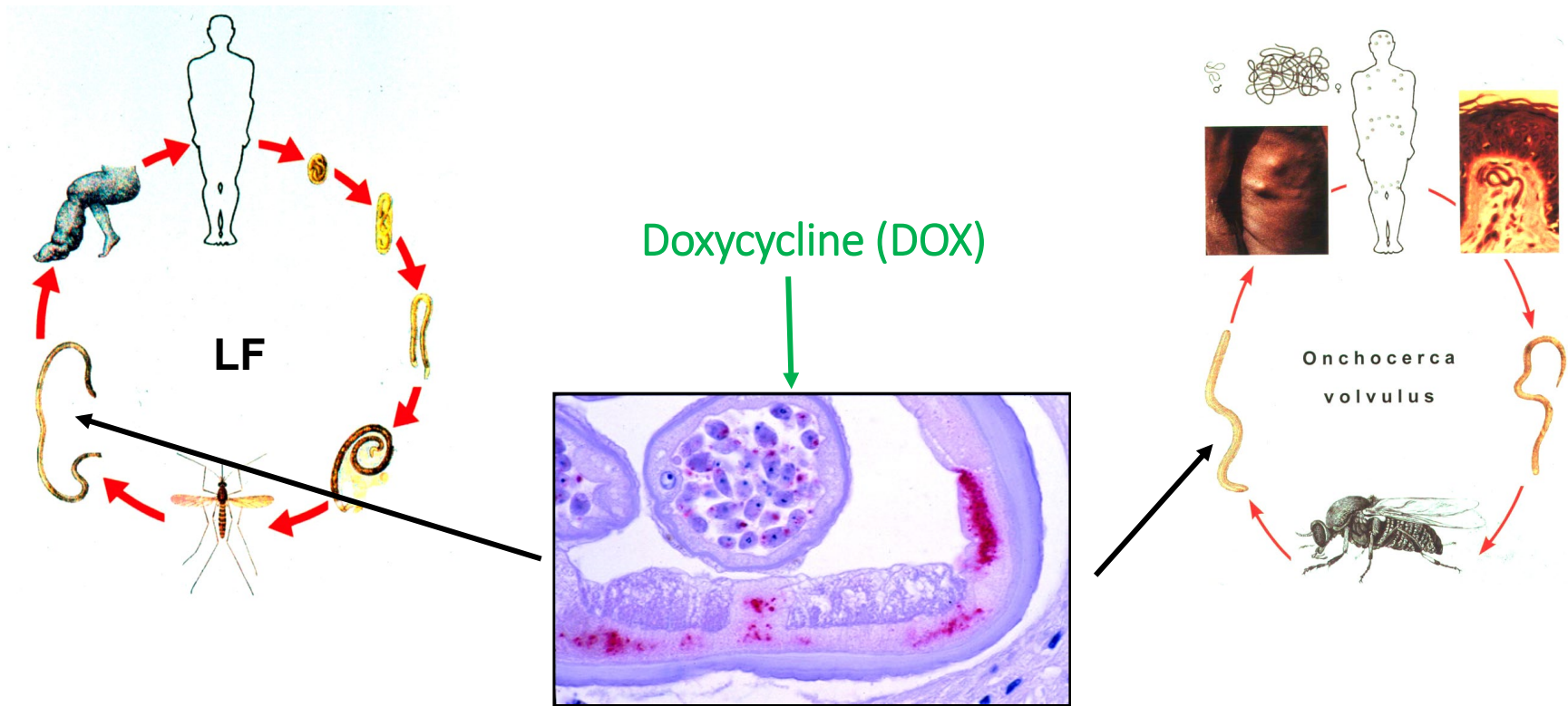


O. volvulus female from an untreated patient



O. volvulus female after 6 weeks of 100 mg/kg doxycycline

From: Hoerauf et al., Lancet 2000



- *Wolbachia* depletion
- female worm sterility after 6-12 months
- growth retardation of the worms
- microfilaricidal effects

Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis

Achim Hoerauf, Lars Volkman, Christoph Hamelmann,
Ohene Adjei, Ingo B Autenrieth, Bernhard Fleischer,
Dietrich W Büttner

THE LANCET • Vol 355 • April 8, 2000

Depletion of wolbachia endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment

Achim Hoerauf, Sabine Mand, Ohene Adjei, Bernhard Fleischer,
Dietrich W Büttner

THE LANCET • Vol 357 • May 5, 2001

Doxycycline in the treatment of human onchocerciasis:
kinetics of *Wolbachia* endobacteria reduction and of inhibition
of embryogenesis in female *Onchocerca* worms

Achim Hoerauf ^{a,*}, Sabine Mand ^a, Lars Volkman ^a, Marcelle Büttner ^a,
Yeboah Marfo-Debrekyei ^b, Mark Taylor ^c, Ohene Adjei ^{b,d}, Dietrich W. Büttner ^{a†}

Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study

Achim Hoerauf • Sabine Specht • Marcelle Büttner • Kenneth Pfarr • Sabine Mand • Rolf Fimmers •
Yeboah Marfo-Debrekyei • Peter Konadu • Alexander Yaw Debrah • Claudio Bandi • Norbert Brattig •
Anna Albers • John Larbi • Linda Batsa • Mark J. Taylor • Ohene Adjei • Dietrich W. Büttner

Med Microbiol Immunol (2008) 197:295–311
DOI 10.1007/s00430-007-0062-1

Newly acquired *Onchocerca volvulus* filariae after doxycycline treatment

Sabine Specht • Achim Hoerauf • Ohene Adjei •
Alexander Debrah • Dietrich W. Büttner

Parasitol Res (2009) 106:23–31
DOI 10.1007/s00436-009-1624-5

Efficacy of 5-week doxycycline treatment on adult *Onchocerca volvulus*

Achim Hoerauf • Sabine Specht •
Yeboah Marfo-Debrekyei • Marcelle Büttner •
Alexander Yaw Debrah • Sabine Mand • Linda Batsa •
Norbert Brattig • Peter Konadu • Claudio Bandi •
Rolf Fimmers • Ohene Adjei • Dietrich W. Büttner

Parasitol Res (2009) 104:437–447
DOI 10.1007/s00436-008-1217-8

Doxycycline Leads to Sterility and Enhanced Killing of Female *Onchocerca volvulus* Worms in an Area With Persistent Microfilaridermia After Repeated Ivermectin Treatment: A Randomized, Placebo-Controlled, Double-Blind Trial

Alexander Yaw Debrah,^{1,2,a} Sabine Specht,^{3,a} Ute Klarmann-Schulz,^{3,4,a} Linda Batsa,² Sabine Mand,³
Yeboah Marfo-Debrekyei,² Rolf Fimmers,⁴ Bettina Dubben,³ Alexander Kwarteng,² Mike Osei-Atweneboana,⁵
Daniel Boakye,⁶ Arcangelo Ricchiuto,^{3,4} Marcelle Büttner,¹ Ohene Adjei,⁸ Charles D. Mackenzie,⁹ and Achim Hoerauf³

CID 2015:61 (15 August)

Comparison of Doxycycline, Minocycline, Doxycycline plus Albendazole and Albendazole Alone in Their Efficacy against Onchocerciasis in a Randomized, Open-Label, Pilot Trial

Ute Klarmann-Schulz^{1,2,3,c}, Sabine Specht^{1,4,c,*}, Alexander Yaw Debrah^{5,6,c}, Linda Batsa⁵,
Nana Kwame Ayisi-Boateng⁷, Jubin Osei-Mensah⁵, Yusif Mubarik⁵, Peter Konadu⁸,
Arcangelo Ricchiuto¹, Rolf Fimmers², Sandra Arriens¹, Bettina Dubben¹, Louise Ford⁹,
Mark Taylor⁹, Achim Hoerauf^{1,3}

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TROPICAL DISEASES 2017

Microbes and
Infection

www.elsevier.com/locate/micinf

2003

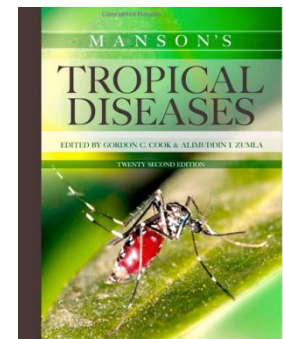
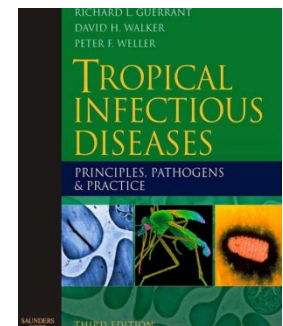
Lymphatic filariasis

- DOX 200 mg/d for 6 weeks if benefit to disease is wanted in addition to macrofilaricidal effect
- DOX 200 mg/d for 4 weeks if focus is on the macrofilaricidal effect

Onchocerciasis

- DOX 200 mg/d for 6 weeks if macrofilaricidal effect is wanted
- DOX 200 mg/d for 4 weeks or 100 mg/d for 5 weeks if only worm sterility is wanted

Hoerauf, Curr Opin Infect Dis 2008,
Taylor-Hoerauf-Bockarie Lancet 2010





ISRCTN68861628 DOI 10.1186/ISRCTN68861628

Comparison of doxycycline alone vs doxycycline plus rifampicin in their efficacy against onchocerciasis

Randomised, placebo-controlled, double-blind trial

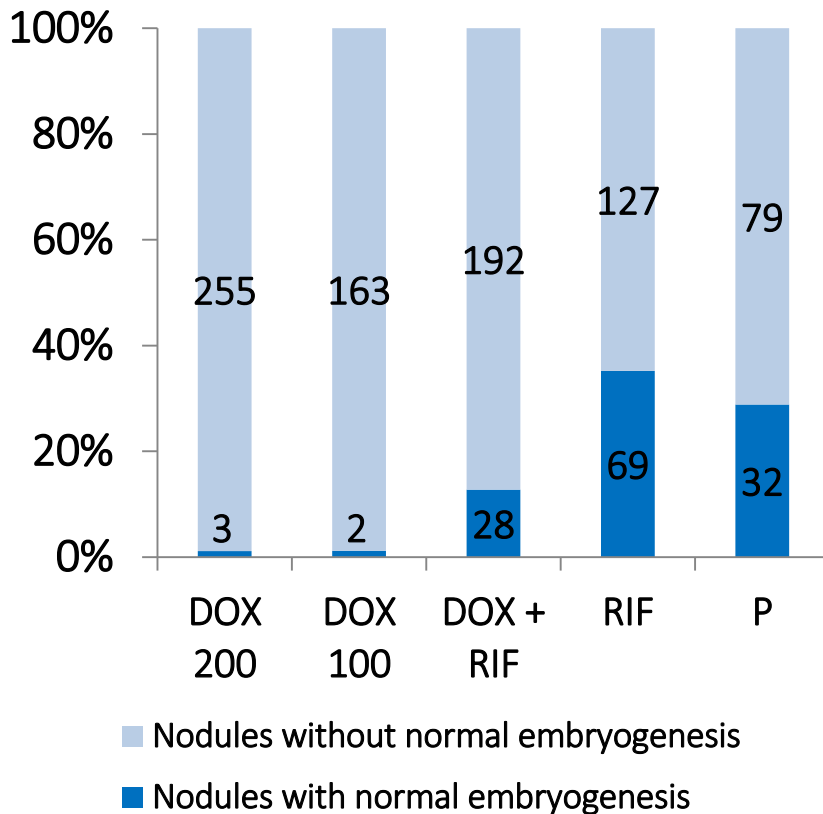
508 patients

5 treatment arms (Doxycycline 200mg/d and 100mg/d for 6 weeks)

Nodulectomies after 6 and 20 months



Doxycycline 100mg for 6 weeks is as good as doxycycline 200mg for 6 weeks to achieve sterility of live female worms.



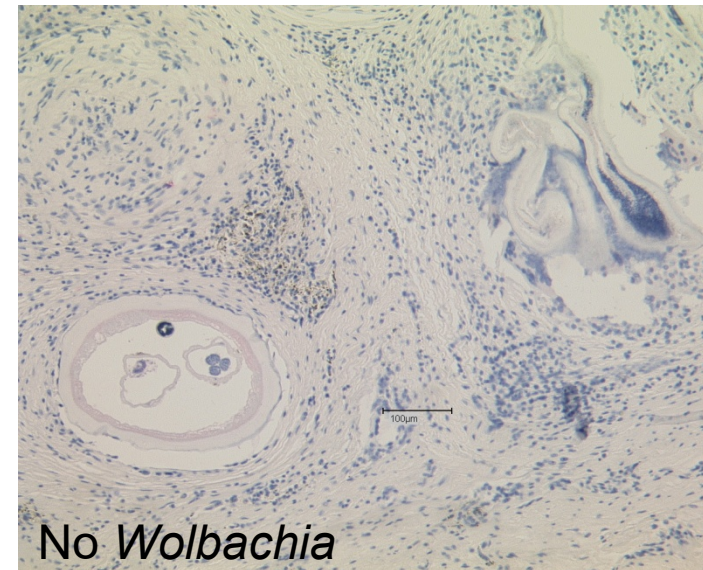
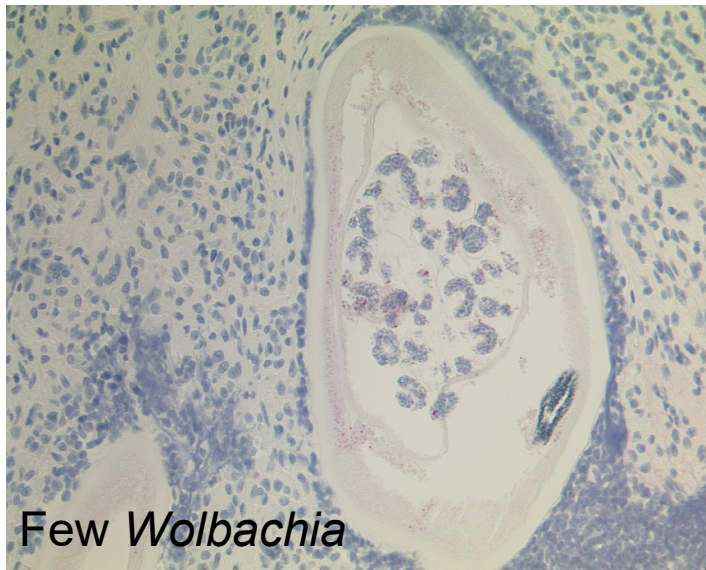
DOX 200 and DOX 100 for 6 weeks:

- Superiority to DOX + RIF for 3 weeks,
- Superiority RIF for 6 weeks
- Superiority to Placebo*

DOX + RIF for 3 weeks:

- Superiority to RIF for 6 weeks
- Superiority to Placebo*

*alternating logistic regression taking the dependency of several nodules in one patient into account (Proc Genmod,SAS®) at an alpha-level of 0.0083 one-sided

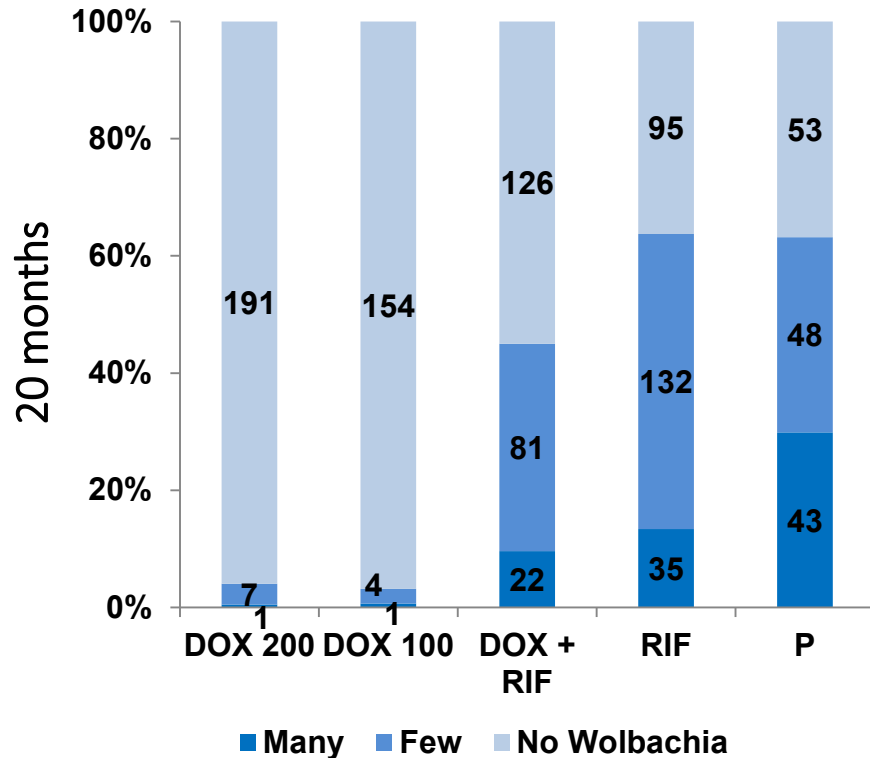


Evaluations

- Worms:
number of *Wolbachia* in worm and uterus, uterus possible (embryonic stages)



Both doxycycline regimens showed complete absence of *Wolbachia* by immunohistology in > 96% of the live female worms, corresponding to the anti-parasitic effect.



DOX 200 and DOX 100 for 6 weeks:

Superiority to DOX + RIF for 3 weeks

Superiority to RIF for 6 weeks

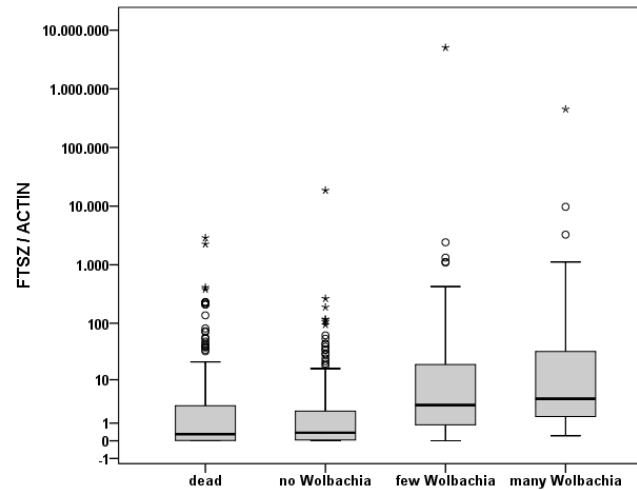
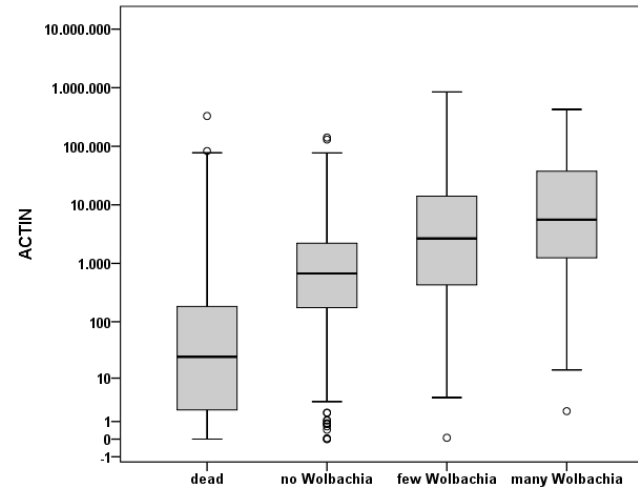
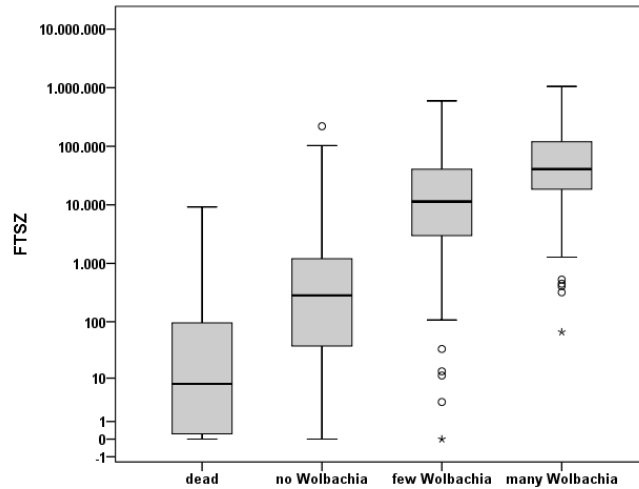
Superiority to Placebo.*

DOX + RIF for 3 weeks:

Superiority to RIF for 6 weeks*

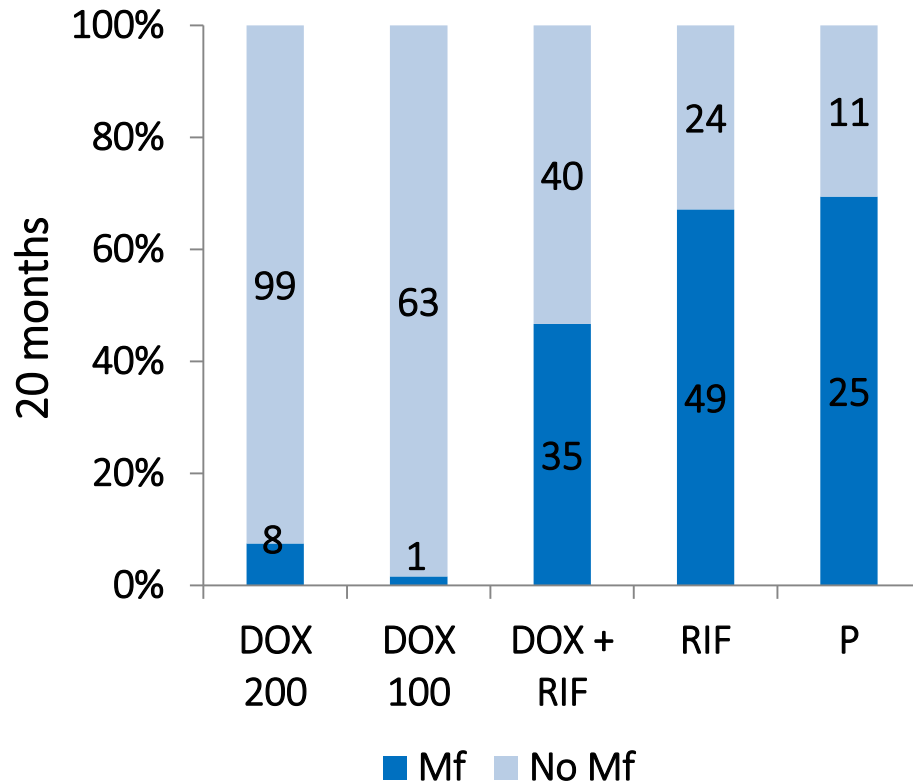
*alternating logistic regression taking the dependency of several worms in one patient into account (Proc Genmod, SAS®) at an alpha-level of 0.0083 one-sided

Histological analysis of *Wolbachia* was confirmed by nodule PCR





Doxycycline 100mg for 6 weeks is as good as doxycycline 200mg for 6 weeks to achieve sustained absence of microfilariae.



DOX 200 and DOX 100 for 6 weeks:

- Superiority to DOX + RIF for 3 weeks,
- Superiority to RIF for 6 weeks
- Superiority to Placebo.*

DOX + RIF for 3 weeks

- Superiority to RIF for 6 weeks*

*Fisher's exact test

RESEARCH ARTICLE

Comparison of Doxycycline, Minocycline, Doxycycline plus Albendazole and Albendazole Alone in Their Efficacy against Onchocerciasis in a Randomized, Open-Label, Pilot Trial

Ute Klarmann-Schulz^{1,2,3e}, Sabine Specht^{1,4e}*, Alexander Yaw Debrah^{5,6e}, Linda Batsa⁵, Nana Kwame Ayisi-Boateng⁷, Jubin Osei-Mensah⁵, Yusif Mubarik⁸, Peter Konadu⁸, Arcangelo Ricchiuto¹, Rolf Fimmers², Sandra Arriens¹, Bettina Dubben¹, Louise Ford⁹, Mark Taylor⁹, Achim Hoerauf^{1,3}

156 patients

5 treatment arms (Doxycycline 200mg/d for 4 weeks)

Nodulectomies after 6 months





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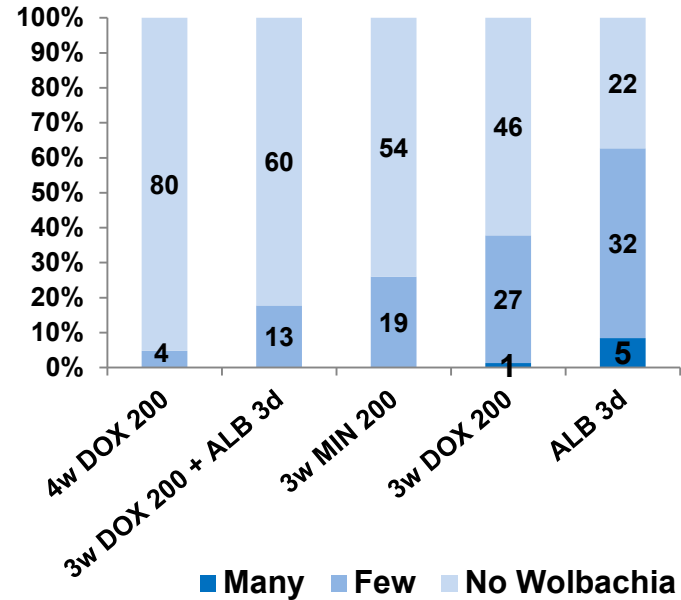
RESEARCH ARTICLE

Comparison of Doxycycline, Minocycline, Doxycycline plus Albendazole and Albendazole Alone in Their Efficacy against Onchocerciasis in a Randomized, Open-Label, Pilot Trial

Ute Klarmann-Schulz^{1,2,3*}, Sabine Specht^{1,4*}, Alexander Yaw Debrah^{5,6*}, Linda Batsa², Nana Kwame Ayisi-Boateng⁷, Jubin Osei-Mensah⁸, Yusif Mubarik⁹, Peter Konadu⁹, Arcangelo Ricchiuto¹, Rolf Fimmers², Sandra Arriens¹, Bettina Dubben¹, Louise Ford⁹, Mark Taylor⁹, Achim Hoerauf^{1,3}

These results confirm earlier studies that DOX 4w is sufficient for *Wolbachia* depletion and the desired parasitological effects.

The data further suggest that there is an additive/synergistic effect of ALB 3d on top of that of DOX 3w alone, and that MIN 3w has a stronger potency than DOX 3w. These latter two results are preliminary and need confirmation in a full randomized controlled phase 2 trial.



Comparison to ALB 3d:

DOX 4w	p < 0.0001 (OR 145)
DOX 3w + ALB 3d	p < 0.0001 (OR 8.2)
MIN 3w	p = 0.0016 (OR 5.8)
DOX 3w	p = 0.0084 (OR 4.2)

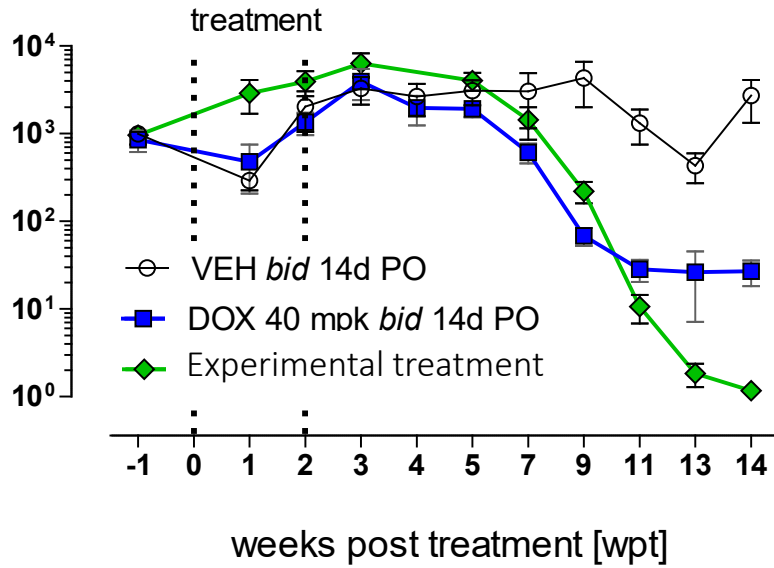
Comparison to DOX 4w:

DOX 3w + ALB 3d	p = 0.0052 (OR 18)
MIN 3w	p = 0.0022 (OR 26)
DOX 3w	p = 0.0007 (OR 36)

No difference between the 3 experimental regimens

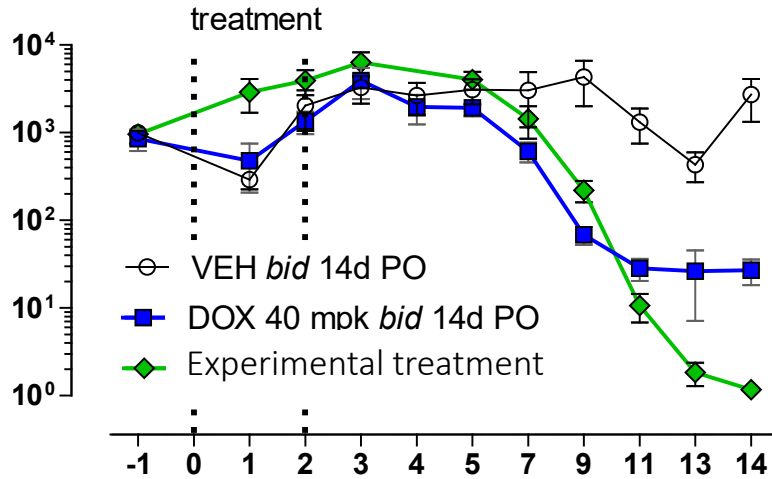
All analyses were done using alternating logistic regression to correct for the possible dependency of the observation on several worms from one patient

L. sigmodontis microfilaremia
(mf+1/10µl blood)



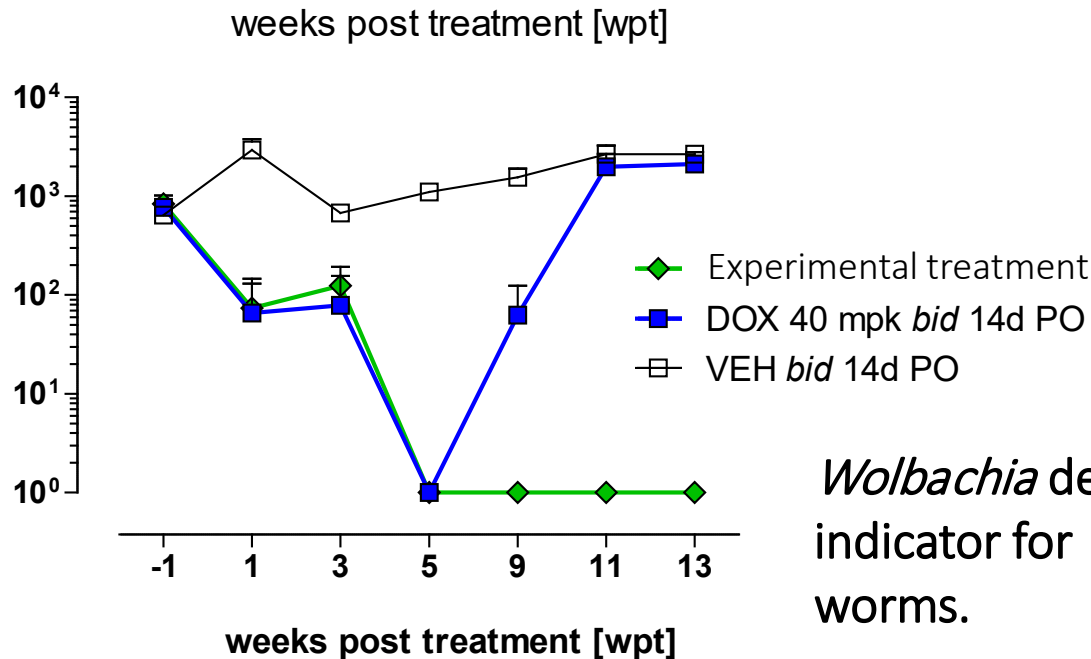
Compound	Reduction % (median)
Experimental	-99.91 vs. VEH
DOX	-97.86 vs. VEH

L. sigmodontis microfilaremia
(mf+1/10µl blood)

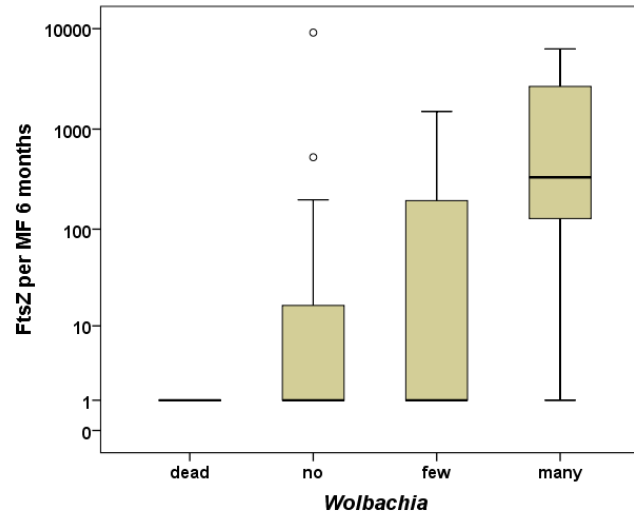
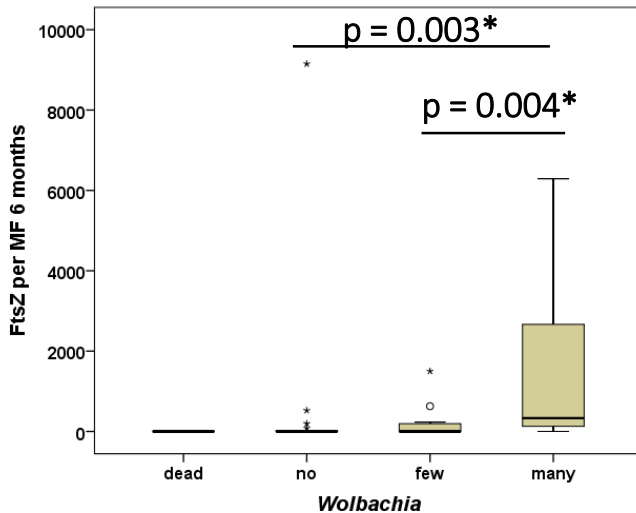


Compound	Reduction % (median)
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Wolbachia FtsZ per microfilaria



Wolbachia depletion in microfilariae is an indicator for *Wolbachia* depletion in adult worms.



	Wolbachia		
	no	few	many
Gültige Anzahl	19	17	12
Mittelwert	527	171	1424
Standardabweichung	2092	379	1902
Minimum	1	1	1
Maximum	9150	1500	6290
Median	1	1	332
Perzentil 25	1	1	128
Perzentil 75	20	193	2665

*Mann-Whitney-U-test (Kruskal-Wallis-test (over all 4 groups): p = 0.003)

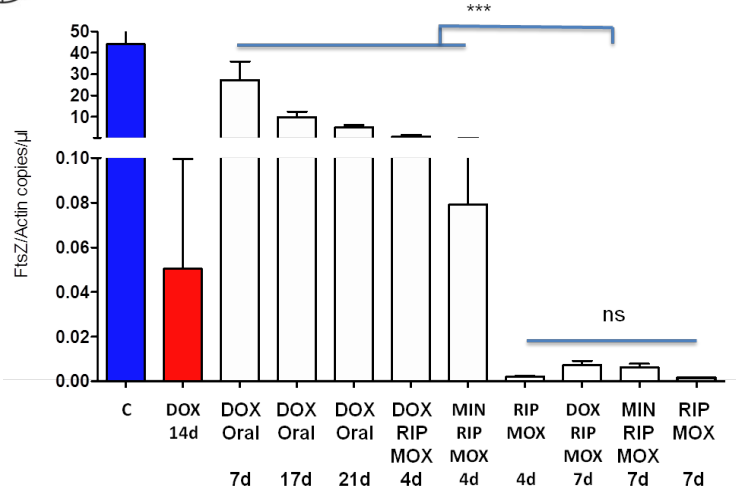
- validated method to detect *Wolbachia* FtsZ/ MF
- reproducible on different days by using the same or a different master-mix
- currently limited to MF-counts > 5MF/sample

- Death or permanent sterilization of the adult onchocerciasis worms
- After 1 course, ~70% (model-based) of treated individuals achieve death or permanent sterilization of all adult onchocerciasis worms
- **All adults and children age ≥ 5** who are infected, excluding pregnant women
- Oral dose, once daily, up to 7 days (DNDi: 14 days) or single, intramuscular injection.
- One dosage for adults, and height-based dosing for children

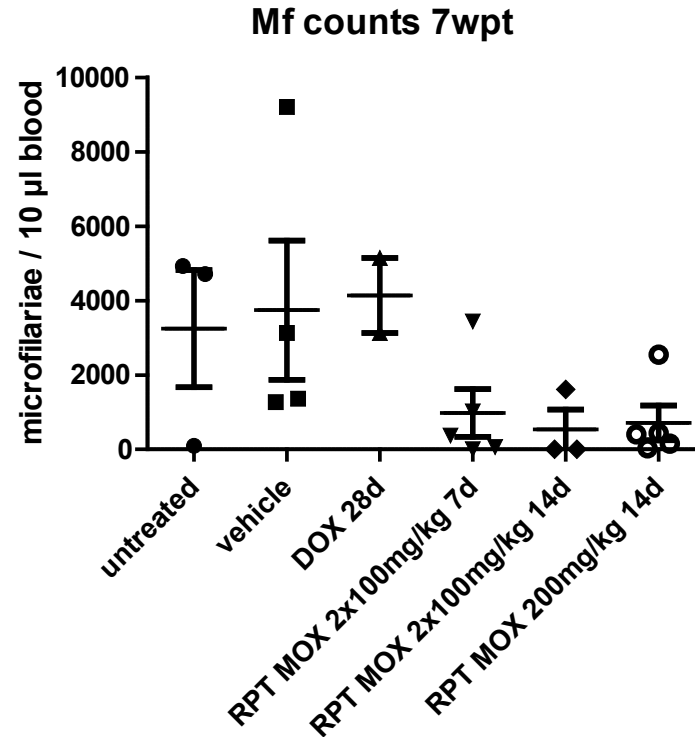


BILL & MELINDA
GATES foundation

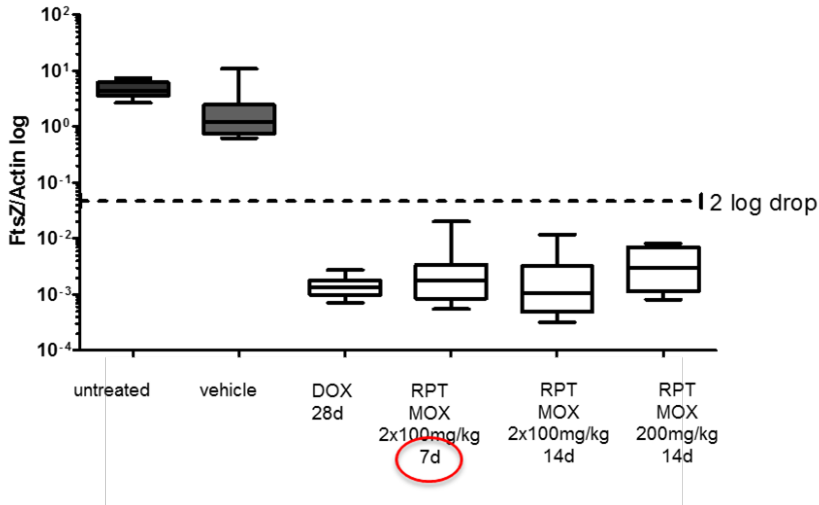
A·WOL Mouse *Litomosoides* Screening
ANTI-WOLBACHIA CONSORTIUM



L. sigmodontis jird model:



L. sigmodontis adult worm
BALB/c WT mouse model:



“The efficacy of Rifapentine 900mg/d plus Moxifloxacin 400mg/d given for 14 or 7 days against Onchocerciasis – a randomized, controlled, parallel-group, open-label, phase II pilot trial.”

In collaboration with:



Interventions*:

Treatment A (experimental): Rifapentine + Moxifloxacin for 14 days

Treatment B (experimental): Rifapentine + Moxifloxacin for 7 days

Treatment C (control): Doxycycline 200mg for 4 weeks

Treatment D (control): Nodulesctomy only

*All participants will be treated with ivermectin (IVM) at the standard MDA dosage of 150 µg/kg following the nodulesctomies 6 months after study onset.

Skin snipping (for Mf-counts/ Mf-PCR): pre-treatment, 3.5 months and 6 months after treatment onset

Nodulesctomies: 6 months after treatment onset

Primary outcome: Absence of *Wolbachia* endobacteria in adult female worms assessed by immunohistology 6 months after treatment onset.

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Primary outcome: Absence of *Wolbachia* endobacteria in adult female worms assessed by immunohistology 6 months after treatment onset.

→ **Recruitment of patients for this trial starts this week**



Drugs for Neglected Diseases *initiative*

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Thanks to all study participants
and thanks for your attention!



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photo: Pavel Desort

Main outcome parameter:

	Onchocerciasis	Lymphatic Filariasis
<i>Wolbachia</i> depletion	<ul style="list-style-type: none"> • Histology of onchocercomata 6 months after treatment onset • Nodule PCR • Mf PCR 	<ul style="list-style-type: none"> • Mf PCR
Fertility of adult female worms	<ul style="list-style-type: none"> • Histology of onchocercomata 20 months after treatment onset 	---
Macrofilaricidal activity	<ul style="list-style-type: none"> • Histology of onchocercomata 20 months after treatment onset 	<ul style="list-style-type: none"> • Filarial Dance Sign (FDS assessed by ultrasonography) • Circulating Filarial Antigen (Filarial test strip (FTS), ICT, Og4C3-Elisa)
Microfilariae (Mf)	Skin snips	Night blood

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→ Onchocerciasis