Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Coulibaly YI, Dembele B, Diallo AA, et al. A randomized trial of doxycycline for *Mansonella perstans* infection. N Engl J Med 2009;361:1448-58.

Supplemental Table 1. Frequency of adverse events

Adverse event*	No Rx (n=110)	Doxy (n=106)	Difference in percent (95% CI)
Dehydration	0	0	0% (-3.8%, 3.5%)
Diarrhea	28 (25.5%)	25 (23.6%)	1.9% (-10.1%, 13.5%)
Fever**	21 (19.1%)	10 (9.4%)	9.7% (0.3%, 19.3%)†
Headache	31 (28.2%)	35 (33.0%)	-4.8% (-17.4%, 7.6%)
Jaundice	0	0	0% (-3.8%, 3.5%)
Lymphangitis	0	1 (0.9%)	-0.9% (-5.7%, 2.6%)
Pruritus	8 (7.3%)	12 (11.3%)	-4.0% (-12.5%, 4.3%)
Rash	3 (2.7%)	1 (0.9%)	1.8% (-2.9%, 7.0%)
Respiratory Sxs	13 (11.8%)	12 (11.3%)	0.5% (-8.7%, 9.6%)
Vomiting	4 (3.6%)	18 (17.0%)	-13.3% (-22.2%, -5.6%)†
$T \geq 38.0^{o}C$	4 (3.6%)	4 (3.8%)	-0.1% (-6.5%, 6.2%)
Hgb < 10 g/dL	0	0	0% (-3.8%, 3.5%)
ALT >45 U/L	0	2 (1.9%)	-1.9% (-7.1%, 1.5%)
Bili > 1.5 mg/dL	32 (29.1%)	13 (12.3%)	16.8% (6.1%, 27.5%)†
Cr >1.4 mg/dL	0	0	0% (-3.8%, 3.5%)

* each subject was counted only once for each adverse event
**by subject report in the preceding 24 hours
† $p<0.05$

Supplemental Table 2. Severity and duration of adverse events in subjects receiving doxycycline.

Adverse event	Grade 1* (no.)	Grade 2* (no.)	Median Duration, Range (days)
Diarrhea	24	1	1, 1-3
Fever	10	0	1, 1-3
Headache	24	11	1, 1-2
Lymphangitis	1	0	1
Pruritus	9	3	1, 1-3
Rash	0	1	27
Respiratory Sxs	5	7	1
Vomiting	17	1	1, 1-5
$T \geq 38.0^{o}C$	3	1	1
ALT >45 U/L	2	0	See below**
Bili > 1.5 mg/dL	9	4	See below**

* Adverse events were graded according to the NCI CTC Toxcity Scale version 2.0, which ranges from 1-5 with 5 being the most severe. No grade 3 or 4 adverse events were reported.

** Bilirubin and ALT were measured at baseline, 21 days, 42 days, at at 6, 12 and 36 months. Elevated ALT resolved in both subjects by 6 months. Bilirubin elevations resolved within 21 days in 4 subjects, within 42 days in 2 subjects, and within 6 months in 5 subjects. Two subjects, one of whom had a mild elevation of bilirubin at baseline (1.67 mg/dl), still had elevated levels at 6 months (< 3 mg/dl). Both resolved by the end of the study.

Supplemental Table 3. Efficacy of doxycycline with and without albendazole/ivermectin in reducing Mp and Wb microfilarial levels

	Median Mp mf/ml (range)				Median Wb mf/ml* (range)				Geometric Mean Wb CAg level** (range)		
	Baseline	6 mo	12 mo	36 mo†	Baseline	6 mo	12 mo	36 mo†	Baseline	6 mo	12 mo
None	323 (17-20,128) n = 75	136 (0-5,916) n = 67	153 (0-11,441) n = 63	264 (0-8,305) n=64	187 (17-6,222) n = 13	68 (0-1547) n =11	179 (0-3056) n = 10	0 (0-44) n=9	1298 (135-14,418) n = 23	1403 (21-2,380,780) n = 20	377 (9-4,315) n=17
Doxy	357 (17-5,712) n = 76	51 (0-1,955) n = 67	0 (0-17) n = 69	0 (0-383) n=64	595 (17-3,196) n = 11	0 (0-187) n = 11	0 (0) n = 11	0 (0-29) n=11	1739 (113-34,153) n = 25	772 (26-101,600) n = 19	679 (95-7,065) n=18
Doxy + AI	332 (17-8,313) n = 30	51 (0-3,315) n = 26	0 (0) n = 25	0 (0-102) n=23	85 (17-8,857) n = 11	0 (0) n = 10	0 (0) n = 10	0 (0-900) n=8	1743 (155-146,305) n = 21	738 (17-124,188) n = 17	277 (31-3,358) n=15
AI	340 (17-6,120) n = 35	102 (0-2,108) n = 31	153 (0-799) n = 27	102 (0-3,783) n=29	51 (17-5,134) n = 11	68 (0-4,539) n = 9	17 (0-1,224) n = 7	0 (0) n=8	1214 (133-61,299) n = 22	501 (8-79,640) n = 15	436 (17-4,630) n=16

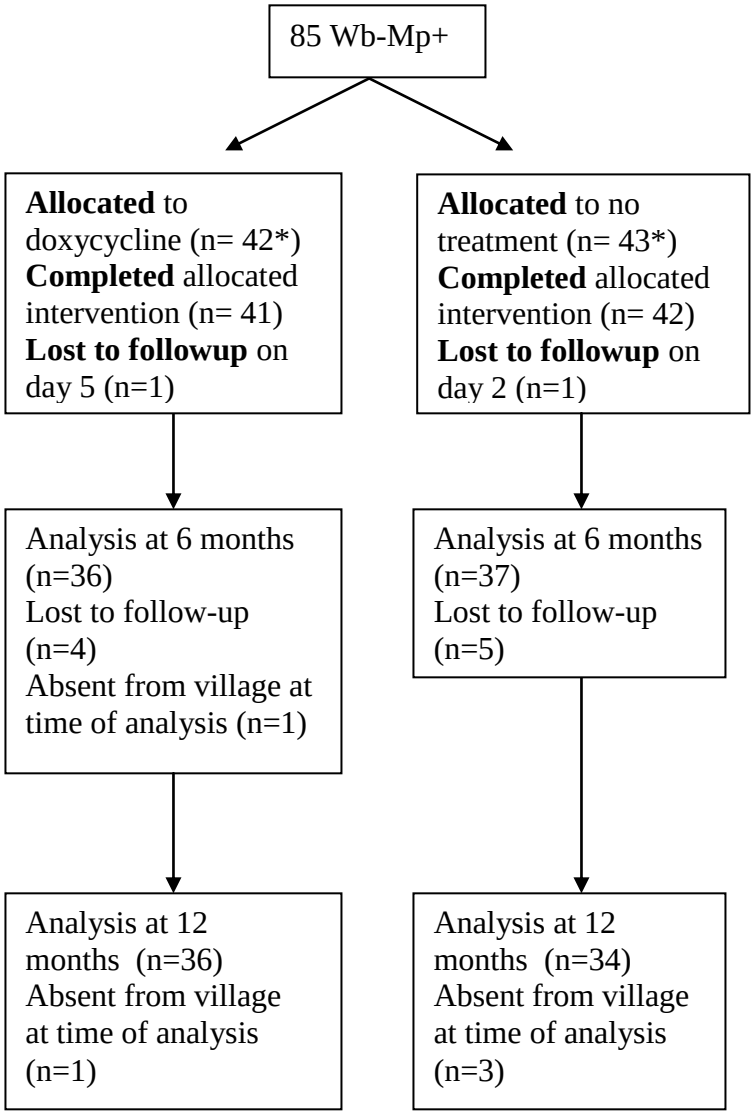
*subjects without detectable Wb microfilariae at baseline have been excluded from analysis

**subjects with negative circulating antigen at baseline have been excluded from analysis

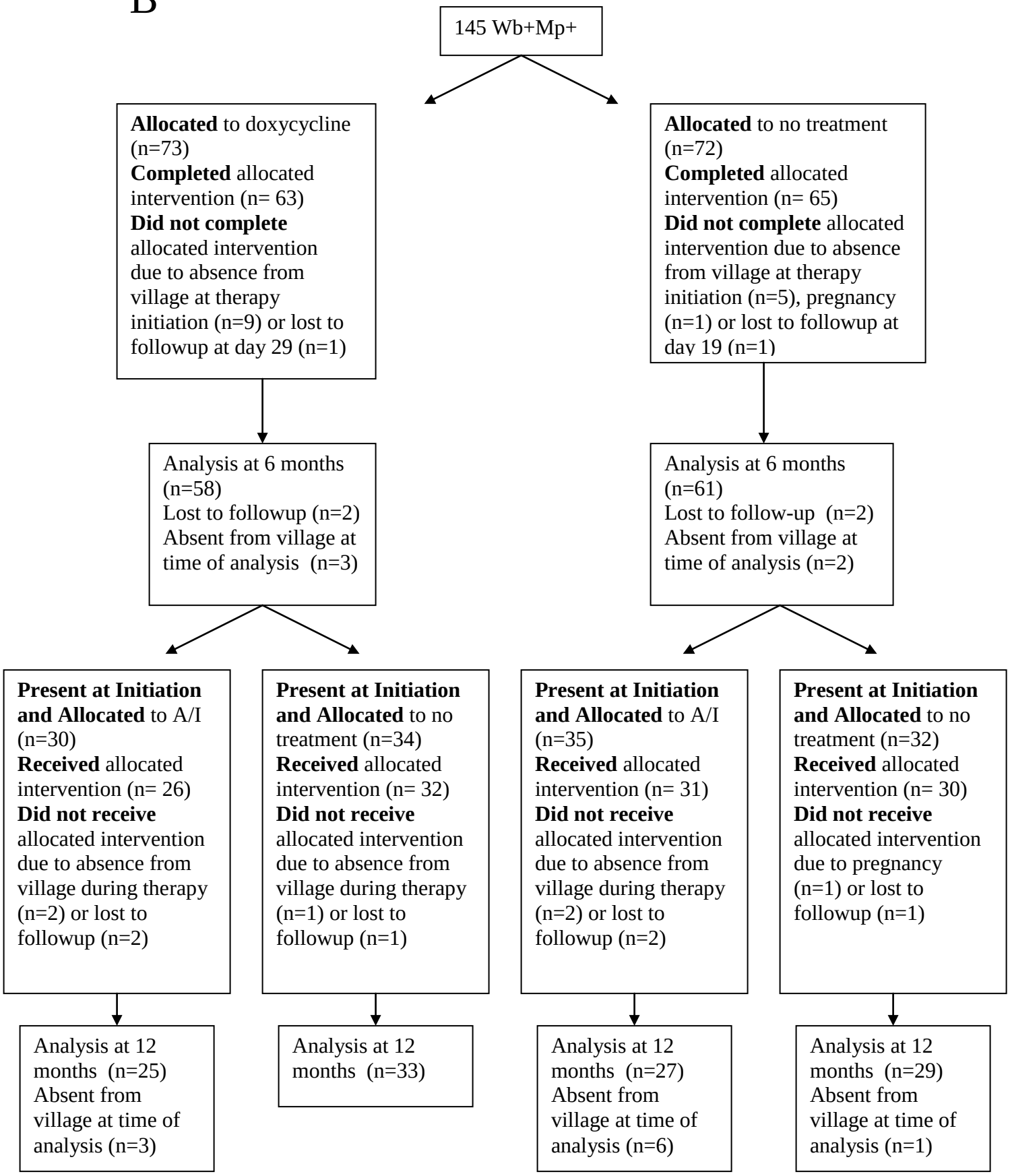
† all subjects received single dose albendazole/ivermectin as part of the mass distribution program prior to the month 36 visit

Supplemental Figure 1. Flow chart of study participants. A) Treatment and analysis of Wb-Mp+ subjects and B) Treatment and analysis of Wb+Mp+ subjects. *Although 40 subjects were anticipated in each of the Wb-Mp+ subgroups, the initial allocation was based on ICT card test results. Five subjects classified as Wb+ by ICT were found to be Wb- by ELISA prior to the initiation of doxycycline therapy and were reallocated to the corresponding Wb-Mp+ treatment group.

A



B


145 Wb+Mp+
Allocated to doxycycline (n=73)
Completed allocated intervention (n= 63)
Did not complete allocated intervention due to absence from village at therapy initiation (n=9) or lost to followup at day 29 (n=1)
Allocated to no treatment (n=72)
Completed allocated intervention (n= 65)
Did not complete allocated intervention due to absence from village at therapy initiation (n=5), pregnancy (n=1) or lost to followup at day 19 (n=1)
Analysis at 6 months (n=58)
Lost to followup (n=2)
Absent from village at time of analysis (n=3)
Analysis at 6 months (n=61)
Lost to follow-up (n=2)
Absent from village at time of analysis (n=2)
Present at Initiation and Allocated to A/I (n=30)
Received allocated intervention (n= 26)
Did not receive allocated intervention due to absence from village during therapy (n=2) or lost to followup (n=2)
Present at Initiation and Allocated to no treatment (n=34)
Received allocated intervention (n= 32)
Did not receive allocated intervention due to absence from village during therapy (n=1) or lost to followup (n=1)
Present at Initiation and Allocated to A/I (n=35)
Received allocated intervention (n= 31)
Did not receive allocated intervention due to absence from village during therapy (n=2) or lost to followup (n=2)
Present at Initiation and Allocated to no treatment (n=32)
Received allocated intervention (n= 30)
Did not receive allocated intervention due to pregnancy (n=1) or lost to followup (n=1)
Analysis at 12 months (n=25)
Absent from village at time of analysis (n=3)
Analysis at 12 months (n=33)
Analysis at 12 months (n=27)
Absent from village at time of analysis (n=6)
Analysis at 12 months (n=29)
Absent from village at time of analysis (n=1)