

Appendix Table 4a. Hydroxyurea Toxicity in Randomized, Controlled Trials in Diseases Other than Sickle Cell Disease

Study, Year (Reference)	Location	Recruitment Period	Inclusion/Exclusion Criteria	Intervention	Starting Dose*	Jadad Score (10)
HIV						
Frank et al., 2004† (66)	North America	Oct 96–Jan 98	Inclusion: Age >18; HIV positive ; ANC >1.0 x 10 ⁹ cells/L , platelet >75 x 10 ⁹ cells/L; Hb >9.2 g/L for men, >8.8g/L for women, CD4 count 0.2–0.7 cells x 10 ⁹ cells/L Exclusion: Preg; renal failure; liver failure; prior HU; pancreatitis; peripheral neuropathy	ddl		4
				HU (low dose) with/without ddl	HU 1000 mg/d	
				HU (high dose) with/without ddl	HU 1500 mg/d	
Havlir et al., 2001 (67)	North America	Nov 98–Jul 99	Inclusion: Age >12 years; HIV positive ; at least 6 mo on IDV, ZDV (or d4T), and 3TC; HIV RNA <200/ml; CD4 count >0.2 cells x 10 ⁹ /L , >0.1 cells x 10 ⁹ /L before starting IDV Exclusion: ANC <1.0 x 10 ⁹ cells/L liver failure AST, ALT >3 ULT, documented or suspected hepatitis; prior treatment with HIV protease inhibitor other than IDV or both ddl and d4T; thrombocytopenia <75 cells x 10 ⁹ /L ; anemia <8.9 for female and 9.1 g/L for men; history of grade 2 or greater peripheral neuropathy	HU IDV ddl d4T	HU 600 BID	2
				IDV ddl d4T + placebo		
				IDV ZDV(or d4T) 3TC		
Swindells et al., 2005 (68)	North America	Sep 99–Apr 07	Inclusion: Age >12; neutrophil count >1.0 x 10 ⁹ cells/L ; HIV-1 RNA 400–100,000 and CD4 count > 0.1 x 10 ⁹ cells/L ; failure of initial antiretroviral treatment; not received non-nucleoside reverse transcriptase inhibitors, ABC or ddl; Hb >9 g/L for women >10 g/L for men; plts > 75 x 10 ⁹ cells/L; estimated creatinine clearance >50mL/min, serum lipase <ULN, serum amylase <1.5x ULN, ALT<5x ULN Exclusion: Preg or breast feeding; acute hepatitis within 6 mo; immunotherapeutic vaccine or cytotoxic agents within 8wks before study start ; hx of pancreatitis or peripheral neuropathy within 2m before study start	ABC/EFV/ddl and HU	HU 500 mg BID	2
				ABC/EFV/ddl		
Seminari et al., 1999 (69)	Europe	Jun 05–Jun 05	Inclusion: Hb >10 g/L; normal amylase; neutrophil >1.5 x 10 ⁹ cells/L ; included if leukopenia included if plt >150 x 10 ⁹ cells/L: absence of current HIV-associated disease or prior hx of any AIDS-defining illness	ddl + HU	HU 500 mg BID	3
				ddl		

Bloch et al., 2006 (70)	Australia	Jan 00–Feb 02	Inclusion: acute primary HIV infection	Indinavir/ritonavir/ddl + (either stavudine or lamivudine) and HU	HU 500 mg BID	2
				Indinavir/ritonavir/ddl + (either stavudine or lamivudine)		
Rutschmann Cluster/HIV						
Rutschmann et al., 1998 (71)	Europe		Inclusion: Age \geq 20 years; HIV positive ; CD4 >0.2 , $<0.5 \times 10^9$ cells/L (twice): two HIV RNA >1000 cells/mL Exclusion: prior HU; pancreatitis; alcohol; peripheral neuropathy; use of d4T	ddl/d4T/HU [‡] ddl/stavudine + placebo	HU 500 mg bid	3
Rutschmann et al., 1998 (72)	Europe		Inclusion: HIV positive ; CD4 $0.22\text{--}0.5 \times 10^9$ cells/L ; HIV RNA >1000 /ml; stavudine and HU naïve Exclusion: > 6 mo of ddl	ddl/stavudine/HU [§] ddl/stavudine	HU 500 mg BID	1
Rutschmann et al., 2000 (73)	Europe		Inclusion: CD4 $0.2\text{--}0.5 \times 10^9$ /L ; HIV RNA $>1000 \times 2$ Exclusion: prior HU; prior stavudine; ddl >6 mo	ddl/stavudine/HU	HU 500 mg BID	2
				Placebo, ddl stavudine		
CML						
Hehlmann et al., 2003 (74)	Europe	Feb 91–Dec 94	Inclusion: newly diagnosed CML in chronic phase Exclusion: prior therapy	HU	40 mg/kg/d	2
				IFN-alpha 2a + HU	IFN 5×10^6 IU/m ² /d + HU added as required	
Benelux CML Study Group, 1998 (75)	Europe	Dec 87–Dec 92	Inclusion: Age \geq 18; previously untreated, newly diagnosed Ph + CML in chronic phase; BCR-ABL (+); WHO performance status 0,1,2: adequate renal/hepatic fxn (bilirubin and creatinine $<2 \times$ ULN) Exclusion: cytogenetic abnl other than -y, + 8 or second 22q-	HU	NR	2
				IFN and HU if needed	3 million units 5x/wk	
Hehlmann et al., 1994 (76)	Europe	Jul 83–Jan 91	Inclusion: newly dx-ed, not pretreated CML in chronic phase; fatigue or weight loss or fever or organomegaly related symptoms or WBC $>50 \times 10^9$ cells/L or Thrombocytosis >1 million Exclusion: Ph(-) or unknown Ph status	HU	40 mg/kg/d	3
				IFN	4 million units/m ²	
				Busulfan	0.1 mg/kg/d	
Broustet et al., 1991 (77)	Europe	May 87 Jul 90	Inclusion: Age >18 ; Ph + CML Exclusion: prior chemo; trisomy 8, isochromosome 17, double Ph +	HU		3
				IFN	4 million U/m ²	

Hehlmann et al., 1993 (78)	Europe	Jul 83–Jan 91	Inclusion: newly diagnosed CML in chronic phase Exclusion: not in chronic phase; no treatment required; prior treatment with IFN or irradiation or cytostatics; lack of consent; second neoplasia; any other reason that made treatment with protocol unlikely	HU	40 mg/kg/d	2
				Busulfan	0.1 mg/kg/d	
Solid Tumor						
Stephens et al., 1984 (79)	North America		Inclusion: advanced prostate cancer (stage D disease) Exclusion: unstable ischemic or rheumatic heart disease; heart failure	HU	3600 mg/m ² , 2days/week	2
				Adriamycin + cyclophosphamide	Adriamycin at 40 mg/m ² and cyclophosphamide at 200 mg/m ² , reduced to AC 20 + cyclophosphamide 100 if in poor-risk group	
Loening et al., 1981 (80)	North America	May 77–Apr 79	Inclusion: histologically proven prostate CA with distant mets and progression	HU	3 g/m ²	2
				Cyclophosphamide	1 g/m ²	
				Methyl-CCNU	175 mg/m ²	
Najejan Cluster/PV						
Najejan and Rain, 1997 (81)	Europe	Jun 05–May 97	Exclusion: age > 65 excluded; previous treatment with radiotherapy; previous treatment with chemotherapy	HU	25 mg/kg/d	2
				Pipobroman	1.25 mg/kg/d	
Kiladjian et al., 2006 ¹ (82)				HU		1
				Pipobroman		
ET						
Harrison et al., 2005 (85)	Europe	Aug 97–Aug 02	Inclusion: Age at least 18 y with ET	HU + aspirin 75 mg/d	HU: 0.5–1g/d	2
				Anagrelide + aspirin 75 mg/d	anagrelide 0.5 mg BID	
Finazzi Cluster/ET						
Finazzi et al., 2000 (83)	Europe	Jun 05–Jun 05	Inclusion: ET; high risk of thrombosis (>60 y or prior thrombosis)	HU	15 mg/kg	2
				No myelosuppressive agent at randomization [#]		
Cortelazzo et al., 1995 (84)	Europe	Apr 90–Aug 93	Inclusion: Age >60; previous thrombosis; plt count <1.5 million	HU	15 mg/kg	2
				None		

* In HIV, only HU doses are given.

† This was a 5-group study, but adverse event data are given for 3 groups (some groups were pooled). These are treatment-naive as well as treatment-experienced patients. Baseline data are reported for all groups combined (listed in arm 1) and were stated to be similar between arms..

* Randomized for 12 weeks then open-label according to response in first 12 weeks.

§ Many patients crossed over after 12 weeks-blinding removed and if poor response (viral load >200 cell/mL) permitted to start HU or dropped if already in HU arm. HU arm had 34 responders, 24 cross-overs after 3 months and 19 remaining in "placebo" arm.

|| See reference 62 for other details of inclusion criteria-this is the same report after 24 months (instead of 12 months).

¶ This is a follow-up of reference 71. Very limited data is given on patients..

Many patients from placebo group crossed over to HU so 79 received HU alone, 15 HU and busulfan, and 20 no chemotherapy.

ANC = absolute neutrophil count; preg = pregnancy; HU = hydroxyurea; ddi = didanosine; IDV = indinavir; d4T = dideoxythymidine; ZDV = zidovudine; 3TC = lamivudine; RNA = ribonucleic acid; AST = aspartate transaminase; ALT = alanine transferase; ULT = upper limit; BID = twice a day; ABC = abacavir; EFV = efavirenz plt = platelet; hx = history; ULN = upper limit of normal; IFN = interferon; CML = chronic myelogenous leukemia; WHO = World Health Organization; NR = not reported; WBC = white blood cells; CA = cancer; CCNU = lomustine; PV = polycythemia vera; ET = essential thrombocytopenia.

Appendix Table 4b. Description of Patient Populations in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease

Study, Year (Reference)	Patient Groups/Intervention	Patients, n	Age, y*	Men, n (%)	Race, %	Time Point of Last Observation
HIV						
Frank et al., 2004 (66)†	ddl	28	NR	(79)	White (38); Black (50); White Hispanic (10)	6 mo
	HU (low dose) with/without ddl	53				
	HU (high dose) with/without ddl	50				
Havlir et al., 2001 (67)	HU IDV ddl d4T	68	NR	(82)	White (69); Black (16); White Hispanic (13)	
	IDV ddl d4T + placebo	68				
	IDV ZDV (or d4T) 3TC	66				
Swindells et al., 2005 (68)	ABC/EFV/ddI and HU	30	38.1; Median, 37 [26–59]	26 (87)	White 16, (53); Black 4, (13); White Hispanic 7, (23); Other 3, (10)	48 wk
	ABC/EFV/ddI	24	39.5; Median, 37 [29–62]	21 (88)	White 13, (54); Black 8, (33); White Hispanic 2, (8); Other 1,(4)	
Seminari et al., 1999 (69)	ddl + HU	40	33.8 [26–47]	26 (65)	NR	40 wk
	ddl	21	31 [21–48]	13 (62)		
Bloch et al., 2006 (70)	Indinavir/ritonavir/ddI + (either stavudine or lamivudine) and HU	35	Median, 36 [31–39]	NR	NR	
	Indinavir/ritonavir/ddI + (either stavudine or lamivudine)	33	Median, 34 [29–40]			
Rutschmann Cluster/HIV						
Rutschmann et al., 1998 (71)	ddl/stavudine/HU	72	NR	NR	NR	24 wk
	ddl/stavudine/placebo	72				
Rutschmann et al., 1998 (72)	ddl/stavudine/HU	72	NR	NR	NR	48 wk
	ddl/stavudine/placebo	72				
Rutschmann et al., 2000 (73)‡	ddl/stavudine/HU	72	NR	NR	NR	24 mo
	ddl/stavudine/placebo	72				

CML						
Hehlmann et al., 2003 (74)	HU	308	Median, 47 [11–83]	(54)	NR	
	IFN-alpha 2a + HU	226	Median, 49 [10–78]	(60)		
Benelux CML Study Group, 1998 (75)	HU	95	Median, 56.4 [27–84]	53	NR	
	IFN and HU if needed	100	Median, 55.7 [20–83]	58		
Hehlmann et al., 1994 (76)	HU	194	46.9; Median, 47 [15–84]	(51)	NR	
	IFN	133	47.4; Median, 47 [18–85]	(66)		
	Busulfan	186	48.5; Median, 49 [17–84]	(61)		
Broustet et al., 1991 (77)	HU	26	58.6	16 (61.5)	NR	
	IFN	24	55.6	15 (62.5)		
Hehlmann et al., 1993 (78)	HU	216	49.2 (unclear mean or median)	(52)	NR	
	Busulfan	225	50.2 (unclear mean or median)	(61)		
Solid Tumor						
Stephens et al., 1984 (79)	HU	69	Median, 64	(100)	White 55, (77); Black 15, (22); Other 2, (3)	
	Adriamycin + cyclophosphamide	68	Median, 65	(100)		
Loening et al., 1981 (80)	HU	40	67.3	(100)	NR	23 mo
	Cyclophosphamide	43	68.8	(100)		
	Methyl-CCNU	38	68.5	(100)		
Najejan Cluster/PV						
Najejan and Rain, 1997 (81)	HU	150	53.2, men; 53.6, women	m/f ratio = 0.89	NR	NR
	Pipobroman	142	55.1, men; 53.3, women	m/f ratio = 1.20		
Kiladjian et al., 2006 (82)	HU	123	NR	NR	NR	
	Pipobroman	134				
ET						
Harrison et al., 2005 (85)	HU + aspirin 75 mg/d	404	Median, 62 [21–88]	180 (45)	NR	
	Anagrelide + aspirin 75 mg/d	405	Median, 61 [23–88]	162 (40)		

Finazzi Cluster/ET						
Finazzi et al., 2000 (83)	HU	56	Median, 67 [40–82]	23.00	NR	
	No myelosuppressive agent at randomization	58	Median, 69 [50–85]	14		
Cortelazzo et al., 1995 (84)	HU	56	Median, 67	23.00	NR	
	None	58	Median, 69	14		

Mean (SD) [range] unless otherwise specified.

† The characteristics represent the whole population (all three arms).

‡ Included 30 patients that crossed over to the HU arm (regrouped the arms as received HU at some point vs not), but do not report the numbers of the placebo arm. Denominators for the outcomes range from 64 to 80, because they used the numbers of patients at the time of the outcome event as denominators.

ddI = didanosine; NR = not reported; HU = hydroxyurea; IDV = indinavir; d4T = dideoxythymidine; ZDV = zidovudine; 3TC = lamivudine; ABC = abacavir; EFW = efavirenz; CML = chronic myelogenous leukemia IFN = interferon; CCNU = Imustine, m/f = male/female.

Appendix Table 4c. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease

Study, Year (Reference)	Intervention	N	Mean Duration of Drug or Follow-up	Deaths, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg Ulcer, n (%)	Rash/Nail Alteration, n (%)	Other, n (%)
HIV												
Frank et al., 2004† (66)	ddl mono	28	6 mo		3 (11)	0	0					Grade 3 chemistry or more: 3 (11)
	HU (low dose) with/without ddl	53			10 (19)	1 (2)	0					Grade 3 chemistry or more: 7 (13)
	HU (high dose) with/without ddl	50			20 (40)*	9 (18)†	3 (6)					Grade 3 chemistry or more: 4 (8)
Havlic et al., 2001 (67)	HU IDV ddl d4T	68	Follow-up: 40 wk	3								GI upset: 2 Pancreatitis: 4 Asymptomatic amylase elevation: 2
	IDV ddl d4T placebo	68		0								GI upset: 1 Pancreatitis: 3
	IDV ZDV (or d4T) 3TC	66		0								
Swindells et al., 2005 (68)	ABC/EFV/ddl and HU	30	Follow-up: 48 wk								5	GI upset: 28 Neurological/psychiatric: 23 Endocrine or metabolic: 7 Arthralgia: 2 Fatigue: 6 Neuropathy: 4
	ABC/EFV/ddl	24									3	GI upset: 10 Neurological/psychiatric: 12 Nasal symptoms: 2 Endocrine or metabolic: 3 Arthralgia: 1 Fatigue: 2 Neuropathy: 1
Seminari et al., 1999 (69)	HU + ddl	40	Follow-up: 40 wk		1	1	1					Hair loss: 2 Hyperamylasemia: 1 Hypertriglyceridemia: 1

	ddl	21	24 wk		0	0	0					GI upset: 1 Hyperamylasemia: 1 Hypertriglyceridemia: 1
Bloch et al., 2006 (70)	Indinavir/ritonavir/ddl + (either stavudine or lamivudine) and HU	35					1					CMV esophagitis: (3) Renal colic: (20) Pneumonia: (3)
	Indinavir/ritonavir/ddl + (either stavudine or lamivudine)	33					0					Neuropathy: (3) Rectal tear: (3) Renal colic: (3)
Rutschmann Cluster/HIV												
Rutschmann et al., 1998 (71)	ddl/stavudine/HU	72	Follow-up: 24 wk		14 [‡]	8 [§]					5	GI upset: 16 Fatigue: 10 Neuropathy: 18 [¶] Diarrhea: 15
	ddl/stavudine/placebo	72			3/25	3					4	GI upset: 11 Fatigue: 2 Neuropathy: 10 Diarrhea: 9
Rutschmann et al., 1998 (72)#	ddl/stavudine/HU	72	12-48 wk48 wk		11/unclear	7						Fatigue: 10 Diarrhea: 15 Paraesthesia: 29
	ddl/stavudine/placebo	72			3 ^{**}	1 ^{††}						Fatigue: 2 ⁺⁺ Diarrhea: 9 ^{§§} Paraesthesia: 14
Rutschmann et al., 2000 (73)#	ddl/stavudine/HU	72	Follow-up: 24 mo		18	29 ^{###}			4 Kaposi sarcoma ^{***}		8	GI upset: 20 ^{†††} Hair loss: 1 Fatigue: 16 Neuropathy: 28 ⁺⁺ Diarrhea: 23 Mucositis: 5
	ddl/stavudine/placebo	72			8	8			1 Kaposi sarcoma		5	GI upset: 6 Hair loss: 1 Fatigue: 5 Neuropathy: 10 Diarrhea: 15
CML												
Hehlmann et al., 2003 (74)	HU	308	Follow-up: 7.3 y								29/30 (9.4)	GI upset: 60 (19.5) (denominator = 304) Flu-like: 38 (12.3) Neurological/psychiatric:

												19 (6.2) Cardiac/pulmonary sx, infections, weight loss, laboratory findings, BM aplasia: 53 (17.2)
	IFN + HU	226	Follow-up: 7.9 y								64/22 (28.3)	GI upset: 88 (38.9) (denominator = 222) Flu-like: 146 (64.6) Neurological/psychiatric: 82 (36.3) cardiac/pulmonary sx: infections: wt. loss: lab findings: BM aplasia: 92 (40.7)
Benelux CML Study Group, 1998 (75)	HU alone	95	Follow-up: 51 mo								1	Fever: 2 accelerated disease/blast crisis: 52
	IFN and HU if needed	100									3	Flu-like: 7 Neurological/psychiatric: 6 Vasculitis: 1 accelerated dz/blast crisis: 37
Hehlmann et al., 1994 (76)	HU	194	Median follow-up: 3.4 y						1 (0.5)			Fever: 1 (0.5)
	IFN	133							2 (1.5)			
	Busulfan	186							2 (1.0)			
Broustet et al., 1991 (77)	HU	26	20.4 mo				0				0	
	IFN	24	13.9 mo				1				1	Flu-like: 1 CNS disturbance: 2 Thyroid insufficiency: 2
Hehlmann et al., 1993 (78)	HU	216	Median follow-up: 2.03 y									Long-lasting BM aplasia: 0 (denominator = 209)
	Busulfan	225										Long-lasting BM aplasia: unknown (denominator = 204)
Solid Tumor												
Stephens et al., 1984 (79)	HU	69	NR				11/68 (16)					
	Adriamycin + cyclophosphamide	68	NR				9/68 (14)					

Loening et al., 1981 (80)	HU	40	NR			2/28 (7)	8/28 (29)					GI upset: 13 (46) (denominator = 28)
	Cyclophosphamide	43				2/34 (5)	11/34 (26)					GI upset: 20 (46) (denominator = 43)
	Methyl-CCNU	38				11/27 (41)	9/27 (33)					GI upset: 11 (41) (denominator = 27)
Najejan Cluster/PV												
Najejan and Rain, 1997 (81)	HU	150	Follow-up: 1 - 17 y					NR by arm ^{§§}	10	12 (9)	10 (7)	GI upset: 9 (7) Myelofibrosis: 26: 40% at the 16th year Cystitis: 3 (2) Stomatitis: 13 (10)
	Pipobroman	142						NR by arm	6 ^{###}	1	5 (4)	GI upset: 19 (17) Myelofibrosis: 3 Stomatitis: 4 (4)
Kiladjian et al., 2006 (82)	HU	123 ^{§§}	Follow-up: 14 y					15				
	Pipobroman	134 ^{§§}	Follow-up: 11 y					25 ^{###}				
ET												
Harrison et al., 2005 (85)	HU + aspirin	404	Median follow-up: 39 mo (12-72)	4 ^{§§§§}				6				Myelofibrosis: 5
	Anagrelide + aspirin	405		3				4				Myelofibrosis: 16 ^{#####}
Finazzi Cluster/ET												
Finazzi et al., 2000 (83)	HU	56	Median follow-up: 73 mo (3-93)						7 (13)			
	No myelosuppressive agent at randomization	58	Median follow-up: 73 mo (12-94)						1 (1.7) ^{***}			
Cortelazzo et al., 1995 (84)	HU	56	27 mo			0		0			0	
	None	58				0		0			0	

* $P = 0.007$ (comparing arms 2 and 3).

† $P = \text{NS}$.

‡ $P = 0.04$ for grade 1, ns for 2, 3, (denominator = 36).

§ $P = 0.03$ for grade 1, ns for 2 and 3.

|| $P = 0.7$.

¶ $P = 0.09$.

n = original assignments please see associated text for number of patients that crossed over.

** $P = 0.04$, (denominator for this outcome unclear given crossover).

†† $P = 0.03$.

‡‡ $P = 0.02$.

§§ $P = 0.2$.

||| $P = 0.008$.

¶¶ $P = 0.08$.

$P = 0.001$.

*** $P = 0.2$.

††† $P = 0.006$.

§§ §Risk = 10% at 13th year (denominator = 150).

||| Risk = 15% at 14th year, Risk = 1.1% per year.

¶¶¶ Risk = 10% at 13th year (denominator = 142).

Risk = 15% at 14th year, Risk = 1.1% per year.

**** $P = 0.0321$.

†††† 6 (40%) occurred after the 12th y of follow-up (denominator = 123).

‡‡‡‡ 11 (44%) after the 12th y of follow-up (denominator = 134).

§§§§ Death from transformation.

||| Unclear why this only represents 157 patients when it is a follow-up of the original study (71). No information on patients lost to follow-up is given.

¶¶¶ (OR 0.67, CI, 0.20-0.33) $P = NS$.

(OR 2.92, CI, 1.24 - 6.86) $P = 0.01$.

ddI = didanosine; HU = hydroxyurea; IDV = indinavir; d4T = didehydrodeoxythymidine; GI = gastrointestinal; ZDV = zidovudine; 3TC = Lamivudine; ABC = abacavir ; EFV = efavirenz; ARV = antiretroviral; CMV = cytomegalovirus; IFN = interferon; BM = bone marrow; CNS = central nervous system; NR = not reported; CCNU = lomustine; PV = polycythemia vera; ET = essential thrombocytopenia; NS = not significant; OR = odds ratio; CI = confidence interval.