WHO/Forum for Collaborative HIV Research Joint Meeting

ARV Drugs Adverse Events, Case Definition, Grading, Laboratory Diagnosis and Treatment Monitoring

BACKGROUND DOCUMENT (DISTRIBUTED)

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INTRODUCTION

Why the need for monitoring toxicities of antiretroviral therapy?
Approximately two million people in the resource-limited setting are now receiving antiretroviral drugs (ARVs), yet very little information is available on drug-related adverse events in this setting. The majority of known drug-related adverse event data are derived from cohort studies or clinical trials conducted in North America, Europe and Australia, and based on innovator drug products. It is vital to gather drug-related adverse event data in the resource-limited setting as different populations are being treated compared to those in resource-rich countries – including more women, pregnant women, children, and those with various co-morbidities and poor nutritional status. In addition, different drugs produced by generic companies, often in fixed-dose combination are being administered.

Adverse event data can be used for program planning and evaluation and to help inform policy and regulatory processes, country or regional treatment guidelines, to provide better information for patient management and to reduce the risk for HIV drug resistance. Currently, gaps exist with respect to policy for collection of data on adverse events in programs, cohort studies and trials. Limited formal pharmacovigilance activities are underway in some resource-limited settings.

A common methodological framework is needed that will include standardized definitions for common adverse events as the first step in achieving more harmonized data collection on treatment-related adverse events and comparability of data across sites and regions. In addition, normative reference ranges for laboratory parameters should be established in the various regions based on local populations to allow for appropriate severity grading of toxicities. This will facilitate the establishment of protocols and management algorithms for monitoring of toxicities in various settings.

What information is currently available on ARV toxicities in resource-limited settings?
The primary sources for information are randomized clinical studies, observational cohort studies and formal pharmacovigilance activities. Together, these sources have the potential to provide a wealth of information from which to glean a better understanding of the effects of ARVs in different populations.

A review of the literature on ARV-related toxicities reported from studies conducted in resource-limited settings in three main regions (Africa, Asia, South America) shows that while numerous studies have been published, a uniform reporting style is lacking, and the location and extraction of toxicity data is difficult. Most publications do not refer to standardized toxicity grading definitions or scales. Some studies report drug-related toxicities of all grades, while others specify only severe toxicities; treatment-limiting effects are not always clearly reported as such. The lack of standardization in ARV toxicity reporting may explain the wide variation observed in the data reviewed. Gender specific susceptibility to certain ARV toxicities may also contribute to the variation in toxicities reported particularly when study designs do not balance the ratio of males to females. In addition, few studies focus on ARV toxicities in children.

In addition to published reports from clinical studies, data on toxicities can be collected from ongoing cohort studies of HIV treatment and by way of formal pharmacovigilance activities underway in various countries and regions, typically based on passive adverse event reporting.

What are the key existing frameworks for terms and definitions?
Several agencies, clinical trials groups and cohorts have developed various classifications, coding and severity grading systems for adverse events in different patient populations (e.g. HIV-infected or HIV-uninfected patients, cancer patients, adults, children), as well as case definitions for specific adverse events. An overview of key sources is provided in the table below.

Overview of selected key frameworks for classifying and defining adverse events

Description	Examples of Sources
Classification and coding of terms	• Medical Dictionary for Regulatory Activities (MedDRA) • WHO Adverse Reaction Terminology (WHO-ART) • International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)
Definitions and coding, clinical trials groups	• Adult AIDS Clinical Trials Group Toxicity Evaluation Group (AACTG TOX-EG) • Pediatric AIDS Clinical Trials Group (PACTG) Appendix 40 • ACTG Appendix 60
Definitions and coding, cohorts	• TREAT Asia HIV Observational Database (TAHOD) data specifications • HIV Cohorts Data Exchange Protocol (HICDEP)
Definitions, for pharmacovigilance activities	• Council for International Organizations of Medical Sciences (CIOMS)/ MedDRA Maintenance and Support Services Organization (MSSO) Standardized MedDRA Queries (SMQs) • Council for International Organizations of Medical Sciences (CIOMS): Reporting Adverse Drug Reactions. Definitions of Terms and Criteria for their Use. 1999.
Severity grading and terminology criteria in different patient populations	• Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events • Agence Nationale de Recherches sur le SIDA et les hépatites virales B et C (ANRS) Table For Grading Severity Of Adult Adverse Events • World Health Organization (WHO): Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. • WHO: Antiretroviral therapy for HIV infection in infants and children : towards universal access. • Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) • Division of Microbiology and Infectious Diseases (DMID) Adult/Pediatric Toxicity Tables • TREAT Asia HIV Observational Database (TAHOD) data specifications v2.1

Where are the gaps?
As this document demonstrates, multiple sources of term classification and case definitions exist that been developed for various purposes by different agencies and groups. There is also a wealth of data available from various sources such as clinical trials and cohort studies. However, in order to assess the extent and nature of toxicities in various settings and relevant populations, a common methodological framework will be needed. As a first step, case definitions for toxicities that are applicable at different levels of health care system with varying infrastructure to assess and conduct diagnostic procedures are needed. In addition, as most criteria for severity grading of toxicities are currently based on normal reference ranges in Western populations, the establishment of laboratory reference ranges by region is important.

In order to provide background information for the development of more standardized case definitions, information on existing definitions in use by various groups for selected adverse events has been collected in this document. In addition, the process for developing standardized definitions will need to incorporate knowledge of the safety profile of drugs and drug classes in different patient populations, overlapping toxicities with other drugs and co-morbidities, consideration of varying clinical skills levels among providers as well as facility and laboratory infrastructures required for diagnostic tests and procedures.

The meeting background documents include the following information:

Section 1: A literature review of reported adverse events from clinical trials and cohort studies of antiretroviral treatment, treatment of TB/HIV co-infection and prevention of mother to child transmission in resource-limited settings

Section 2: A literature review of normative laboratory reference ranges that have been established in different regions around the world

Section 3: Major documents that have been sourced for existing definitions and toxicity grading criteria of adverse events and a list of major adverse events to be defined that have been identified based on initial expert consultations

Section 4: A review of definitions for commonly reported treatment-related adverse events obtained from selected major sources (outlined in Section 3)

Section 5: Preliminary results from a pilot survey questionnaire on monitoring of toxicities distributed to several sites in resource-limited settings

SECTION I
Literature Review: Antiretroviral treatment-related toxicities

I: Review of toxicities reported for antiretroviral treatment regimens

Background: Without a standardized reporting protocol, HIV drug toxicity monitoring in resource-limited settings is restricted to piecemeal reports from clinical trials, cohort and cross-sectional studies. By compiling and reviewing published literature, a snapshot of the most common antiretroviral therapy (ARV) drug toxicities was estimated and used to compare the occurrence of adverse drug effects in different regions.

Methods: A primary electronic literature search was conducted of published clinical trials, cohort and cross-sectional studies as well as select review articles presenting adverse event data related to antiretroviral drug therapies in three resource-limited regions: South America, Southeast Asia, and Africa. PubMed searches using the key words "adverse event + antiretroviral" "HIV + toxicity" "adverse effect" "resource limited" in combination with "Africa/Asia/India/South America" generated relevant peer-reviewed articles which were examined and included in a matrix if specific cases of drug related toxicities were counted and reported. Review article reference documents were obtained when relevant. Web searches of cohorts, HIV conferences, and author searches also aided in identifying published literature. All research was restricted to articles written in English and published in journals accessible through the George Washington University online library or free of charge from the National Library of Medicine online journals.

40 publications were included in a literature summary matrix (Section 1.2), with publication dates ranging from 1999 to 2007. Drug regimens attributed to specific toxicities are not addressed at length in this report, however all drug regimen information is contained in the summary matrix (Section 1.2). For comparison purposes, drug toxicities were recorded as proportion of the population under study who experienced the event (prevalence), without time factor consideration. To compare individual toxicity prevalence between regions, all study toxicity reports were combined and used to calculate mean toxicity prevalences for each resource-limited setting. This allowed for ranking of the most commonly observed and reported ARV toxicities in each region. In addition, the ranges of values reported by studies were included to show the variation of observed toxicity occurrence. Studies were further distinguished based on the identification of toxicities leading to treatment substitution or discontinuation, referred to as "treatment-limiting" toxicities.

Results: A total of 36 relevant articles reporting ARV toxicities in adults (2 from South America, 14 from Southeast Asia, and 20 from Africa) were included in the summary matrix.

The predominant ARV treatment-limiting toxicities reported in South America were gastrointestinal, hematologic toxicities and neuropathy; in Southeast Asia were lipodystrophy, rash and hepatitis; in Africa were neuropathy, neutropenia and lipodystrophy. The most prevalent toxicities not resulting in treatment discontinuation or drug switching were lipodystrophy, dyslipidemia and nervous system disorders in Southeast Asia; lipodystrophy, nervous system disorders and rash in Africa. South American studies were limited to toxicity reporting resulting in treatment alteration. Overall, wide variation existed in the prevalence and types of toxicities reported. Standardized toxicity definitions or grading systems were clearly referenced in only 14 (34%) of the articles. The most frequently referenced grading scale was the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, Table for Grading the Severity of Adult and Pediatric Adverse Events. Other studies relied on subjective physician or researcher toxicity assessment, patient self-report, or toxicity scales and definitions without reference.

Treatment-limiting effects varied substantially when comparing between the three regions. While both South American and African study groups stopped or switched treatment regimens due to neuropathy, in some reports Africa had nearly twice the frequency of neuropathy compared to South America. Two of the most common toxicities reported in African groups included neuropathy and neurological effects. Most studies used "neuropathy" to indicate peripheral neuropathy and "neurological effects" to classify dizziness, headaches, and sleep disturbances.

Both Africa and South America had similar reported prevalences of ARV drug-induced hepatitis or hepatic toxicity (mean of 1.5%, range of 0.1 to 6% and mean of 1.1%, range of <1 to 1.2% respectively), while reported prevalence in Southeast Asia was much higher (mean of 7.2%, range of 2.2 to 12.2%) Southeast Asia populations most frequently interrupted ARV treatment due to lipodystrophy. Though not treatment-limiting, some Southeast Asia studies reported a high prevalence of dyslipidemia, which often accompanies lipodystrophy. Reporting of lipodystrophy that was not treatment-limiting ranged widely in studies from Southeast Asia and Africa, with prevalence rates of less than 5% to more than a quarter of the study populations. African studies referenced here did not report any dyslipidemia. Reported prevalence of treatment-limiting rash was also similar between Southeast Asia (mean of 9.25%, range of 1-14.6%) and Africa (mean of 4.6%, range of 0.9-14%), though much lower in South America (mean of 3.3%, range of <1 to 9.3%).

Five articles reported ARV-related toxicities in children (1 South American, 1 Southeast Asian, and 3 African). The study from South America noted treatment-limiting anemia related to zidovudine, gynecomastia and hepatitis due to efavirenz and nevirapine rash specifically in children (<13 years old). One study from Thailand reported a high occurrence

(23%) of grade 2 rash (grading according to DAIDS toxicity table) in children receiving nevirapine-based ARV regimens and transient grade 1 CNS disturbances (26%) in children receiving efavirenz-based ARV regimens, though neither toxicities were treatment-limiting. Studies from Africa generally reported low occurrence of ARV toxicities in children, with rash due to nevirapine or efavirenz and increased liver enzymes as the most commonly reported.

Table 1. Summary of the most common ARV toxicities reported in studies from three regions*º

	South America			Southeast Asia			Africa		
ARVs	**(n=5,369)**			**(n=6,890)**			**(n=10,862)**		
	Toxicity	Mean % (range)	# of Studies referenced	Toxicity	Mean % (range)	# of Studies referenced	Toxicity	Mean % (range)	# of Studies referenced
Treatment-limiting	**Gastrointestinal**	8.2 (4.6-11.8)	1	**Lipodystrophy**	31.7	1	**Neuropathy**	14 (0.7-35)	8
	Hematologic	6.9	1	**Rash**	9.25 (1-14.6)	4	**Neutropenia**	7.7 (2-17.3)	6
	Neuropathy	6.8	1	**Hepatitis**	7.2 (2.2-12.2)	2	**Lipodystrophy**	6.2	3
Not Treatment-limiting				Dyslipidemia	46.4 (34.5-55.8)	3	Lipodystrophy	34.2	1
				Lipodystrophy	29.2 (3.5-66.1)	6	Neuropathy	23 (0.6-75)	5
				Rash	10.6 (6.6-14.3)	6	Neurological	16.5 (10-23)	1
				GI/nausea/vomiting	9.5 (5-15.5)	2	Rash	13.6 (1-26)	3

* See Appendix X for full listing of studies and drug regimens represented here
º See Bibliography for references; Ia South America, Ib. Southeast Asia, Ic. Africa

II: Review of toxicities reported in treatment of HIV-TB coinfection

Background: Many patients receiving antiretroviral therapies in resource-limited settings have tuberculosis (TB) co-infections. These concomitant regimens may result in specific toxicities that should be monitored along with general ARV related adverse effects.

Methods: A second exploratory electronic search was conducted to assess the extent of literature reporting drug toxicities due to ARVs in combination with tuberculosis treatment. PubMed searches using the key words "tuberculosis" in combination with "ARV" or "toxicity" were identified and reviewed if the studies were conducted in resource-limited areas of South America, Southeast Asia, or Africa.

Seven publications were included in a literature matrix (Section 1.3) with publication dates ranging from 2004 to 2007. For comparison purposes, drug toxicities were recorded as proportion of the population under study who experienced the event (prevalence), without time factor consideration. To compare individual toxicity prevalence between regions, all study toxicity reports were combined and used to calculate mean toxicity prevalences for each resource-limited setting. This allowed for ranking of the most commonly observed and reported toxicities in each region. In addition, the ranges of values reported by studies were included to show the variation of observed toxicity occurrence. A further distinction noted was the identification of toxicities leading to treatment substitution or discontinuation, referred to as "treatment-limiting."

Results: A total of 7 articles (2 from South America, 2 from Southeast Asia, and 3 from Africa) published between 2004 and 2007 reporting toxicities related to tuberculosis (TB) and concomitant ARV regimens were included in the matrix for analysis. The predominant TB/ARV treatment-limiting toxicity in South America was toxic hepatitis followed by elevated liver enzyme levels, leukopenia, nausea and vomiting; while common non-treatment limiting toxicities were neuropsychological and immune reconstitution syndrome with associated lymph node enlargement. Dual TB/ARV regimen treatment-limiting toxicities in Southeast Asia were primarily due to anemia, hepatitis, and rash, while a large proportion of non-treatment limiting toxicities were neurological. One African study reported neutropenia to be the most common treatment-limiting toxicity when ARVs were administered with TB drugs. Non-treatment limiting toxicities in African studies were mainly fatigue, neurological, rash and abdominal pain. Three of the seven articles referenced the AIDS Clinical Trials Group (ACTG) toxicity grading standards, while the others did not clearly reference an established toxicity scale.

Hepatitis was the most common treatment limiting ARV/TB toxicity in both South America and Southeast Asia, though neutropenia was highest in Africa. Hepatic toxicity was noted in one African study of concomitant ARV/TB drug regimens, though it was not treatment limiting and was observed much less often than South American reports (prevalence of 11% compared to a mean of 18.3% respectively). Though grade 3 or 4 leukopenia was reported in one South American study, leukopenia was not observed or reported in either Southeast Asia or Africa studies. Both South American and African study populations experienced treatment-limiting nausea and vomiting in response to ARV/TB regimens, but prevalence in South America was double the estimated prevalence in Africa; while Southeast Asia had similar nausea and vomiting prevalence to Africa, effects were not treatment-limiting. All three regions reported neurological or neuropsychological toxicities, though one African study reported a prevalence exceeding the other two regions (40% compared to 14.3% and 16.5% respectively).

Table 2. Summary of the most common ARV+TB drug toxicities reported in studies from three regions*º

	South America			Southeast Asia			Africa		
TB+ARV	**(n=81)**			**(n=284)**			**(n=922)**		
	Toxicity	Mean % (range)	# of Studies referenced	Toxicity	Mean % (range)	# of Studies referenced	Toxicity	Mean % (range)	# of Studies referenced
Treatment-limiting	**Toxic hepatitis**	18.3 (5.6-31)	1	**Anemia**	10.3	1	**Neutropenia**	11.8	1
	Leukopenia	17	1	**Hepatitis**	13.5	1	**Neuropsychological**	5	1
	Elevated liver enzymes	15.5 (14-17)	1	**Rash**	6.9		**GI/nausea/ vomiting**	5	1
	Nausea and vomiting	14	1				**Abdominal pain**	5	1
Not Treatment-limiting	Neuropsychological	14.3	1	Neurological	16.5 (12.7-20.2)	1	Fatigue	45	1
	Immune reconstitution inflammation syndrome	14.3	1	GI/nausea/vomiting	5.9 (3.9-7.9)	1	Neurological	40	1
	IRIS lymph node enlargement	12.2	1	Neuropathy	4.4 (3.1-5.6)	1	Rash	15	1
				Rash	3.3 (0.8-6.9)	2	Abdominal pain	15	1

* See Appendix X for full listing of studies represented here
º See Bibliography for references; IIa. South America, IIb. Southeast Asia, IIc. Africa

III: Review of toxicities for regimens to prevent mother to child transmission

Background: Many female patients receiving antiretroviral therapies in resource-limited settings have additional drug complications during pregnancies requiring HIV transmission prophylaxis. These regimens may result in specific toxicities that should be monitored along with general ARV related adverse effects.

Methods: A third exploratory electronic search was conducted to assess the extent of literature reporting drug toxicities due to antiretrovirals used as prophylaxis in prevention of mother-to-child HIV transmission (PMTCT). PubMed searches using key words "PMTCT" in combination with "ARV" or "toxicity" were identified and reviewed if the studies were conducted in resource-limited areas of South America, Southeast Asia, or Africa.

Ten publications were included in a literature matrix (Section 1.4) with publication dates ranging from 1999 to 2007. For comparison purposes, drug toxicities were recorded as proportion of the population under study who experienced the event (prevalence), without time factor consideration. To compare individual toxicity prevalence between regions, all study toxicity reports were combined and used to calculate mean toxicity prevalences for each resource-limited setting. This allowed for ranking of the most commonly observed and reported toxicities in each region. In addition, the ranges of values reported by studies were included to show the variation of observed toxicity occurrence. A further distinction noted was the identification of toxicities leading to treatment substitution or discontinuation, referred to as "treatment-limiting." Maternal and infant toxicities were compared separately across regions.

Results: A total of 10 relevant articles (2 from South America, 3 from Southeast Asia, and 5 from Africa), published between 1999-2007, reported maternal and infant toxicities related to HIV mother-to-child transmission ARV prophylaxis. Maternal treatment-limiting toxicities observed in the South American studies included mainly low hemoglobin (though possibly due to blood loss during delivery), skin rash, and liver function abnormalities. Non treatment-limiting maternal toxicities commonly noted were prenatal anemia and skin rash. South American infants on ARV prophylaxis displayed anemia and neutropenia. The dominant maternal treatment-limiting toxicities in the Southeast Asia studies were rash, persistent neutropenia, and hepatotoxicity. Though not treatment-limiting, a large proportion of mothers receiving nevirapine experienced rash or hepatotoxicity while mothers receiving zidovudine (AZT) had postpartum anemia and raised liver enzymes. Southeast Asia infants on ARV prophylaxis experienced neutropenia and low haematocrit levels. Only one study reported maternal treatment-limiting effects of PMTCT drug regimens in Africa. Treatment-limiting skin toxicity and anemia were observed in response to nevirapine, and women with

higher baseline CD4 cell counts also experienced treatment-limiting hepatic toxicities. Non treatment-limiting African maternal toxicities were mainly neuropathy, anemia, rash and hepatic toxicity. Infants in these studies showed primarily hepatic toxicities and rash with some anemia and neurological effects. Eight of the ten articles referenced established toxicity grading scales, half referred to the AIDS Clinical Trials Group (ACTG) while half referred to Division of AIDS, National Institute of Allergy and Infectious Diseases (DAIDS).

Rash and hepatic toxicities were responsible for most of the maternal PMTCT drug regimen substitutions and discontinuations in all three regions. Southeast Asia had the highest reported maternal rash and hepatic toxicity prevalence, however most did not result in treatment interruption. Only African studies reported maternal neuropathy, and while a large proportion of tested mothers were observed with anemia (up to 23%), most did not change drug regimens. One South American study reported anemia affecting the majority of infants treated with ARVs (73.5%). In comparison, African studies found much smaller prevalence of infants with anemia, though Africa was unique in observing and reporting infant hepatotoxicity, rash and neurological toxicities.

Table 3. Summary of the most common PMTCT toxicities reported in studies from three regions*°

	South America			Southeast Asia			Africa		
PMTCT	**(n=236 mothers, 34 infants)**			**(n=727 mothers, 483 infants)**			**(n=3,072 mothers, 2,947 infants)**		
	Toxicity	Mean % (range)	# of Studies referenced	Toxicity	Mean % (range)	# of Studies referenced	Toxicity	Mean % (range)	# of Studies referenced
	Mothers			***Mothers***			***Mothers***		
Treatment-limiting	**Low hemoglobin (?)**	5.1	1	**Rash**	7	1	**Hepatotoxicity**	6	1
	Rash	2	1	**Neutropenia**	5.9	1	**Anemia**	3	1
	Liver function abnormalities	1	1	**Hepatotoxicity**	4.9	1	**Skin toxicity**	3 (1-5)	1
Not Treatment-limiting	Rash	1.5	1	Rash	26.5 (22.7-30.3)	1	Neuropathy	12.3 (1-18)	1
	Prenatal anemia	*	1	Hepatotoxicity	26.7 (24.4-28.9)	1	Anemia	12.1 (0.3-23)	2
				Postpartum anemia	6.9	1	Rash	5.9 (1.3-10)	3
				Elevated liver enzymes	4.3	1	Hepatotoxicity	4.4 (0.7-9)	2
Not Treatment-limiting	***Infants***			***Infants***			***Infants***		
	Anemia	73.5	1	Low haematocrit	1	1	Hepatotoxicity	15.6 (9.4-21.7)	1
	Neutropenia	14.7	1	Neutropenia	*	1	Rash	12.6 (2.9-26.2)	2
							Anemia	3.6 (2.9-4.2)	1
							Neurological	3.3 (2-4)	1

* numbers not reported
(?) may be due to blood loss during delivery

* See Appendix X for full listing of studies represented here
° See Bibliography for references; IIIa. South America, IIIb. Southeast Asia, IIIc. Africa

Conclusion: Articles publishing ARV toxicity results pertaining to resource-limited settings lacked a uniform reporting style, which made locating and extracting toxicity data difficult. Published antiretroviral safety and toxicity reporting from South America in general is limited. Most of the articles referenced in this review did not use standardized toxicity grading definitions or scales. Of those that did, the Division of AIDS, National Institute of Allergy and Infectious Diseases, Table for Grading the Severity of Adult and Pediatric Adverse Events was most frequently referenced. Some studies reported drug-related toxicities of all grades, while others specified only severe toxicities; treatment-limiting effects were not always clearly reported as such. Lack of standardization in ARV toxicity reporting may explain the wide variation in the data summarized here. Because of these important constraints, only limited conclusions can be drawn from the comparisons between the various settings.

In addition, few studies were found focusing on ARV toxicities in children. The male to female ratio of the studies was also not consistent. Overall, studies conducted in Southeast Asia were dominated by male participants, while studies conducted in Africa tended to have slightly higher numbers of female participants. Some gender specific susceptibility to certain ARV toxicities likely contributes to the variation in toxicity reporting observed between regions when study designs do not balance the ratio of males to females.

Next steps: Ideally, a standardized set of toxicity definitions and reporting procedures will be established and implemented worldwide by researchers. With more uniform reporting of agreed upon toxicity definitions, future research may begin to explore and explain the variation in types and prevalence of ARV related toxicities presented here in various regions. Future research should consider genetic and gender influences on susceptibility to specific toxicities when comparing populations in different regions receiving similar ARV drug regimens.

Bibliography

I. Review of toxicities reported for antiretroviral treatment regimens

Ia. South America

Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med*. Dec 1 2005;353(22):2325-2334.

Wolff MJ, Beltran CJ, Vasquez P, et al. The Chilean AIDS cohort: a model for evaluating the impact of an expanded access program to antiretroviral therapy in a middle-income country--organization and preliminary results. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2005;40(5):551-557.

Ib. Southeast Asia

Anekthananon T, Ratanasuwan W, Techasathit W, Sonjai A, Suwanagool S. Safety and efficacy of a simplified fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR) for the treatment of advanced HIV-infected patients: a 24-week study. *J Med Assoc Thai*. Jul 2004;87(7):760-767.

Chang KH, Kim JM, Song YG, Hong SK, Lee HC, Lim SK. Does race protect an oriental population from developing lipodystrophy in HIV-infected individuals on HAART? *J Infect*. Jan 2002;44(1):33-38.

Chuapai Y, Kiertiburanakul S, Malathum K, Sungkanuparph S. Lipodystrophy and dyslipidemia in human immunodeficiency virus-infected Thai patients receiving antiretroviral therapy. *J Med Assoc Thai*. Mar 2007;90(3):452-458.

Ho TT, Chan KC, Wong KH, Lee SS. Indinavir-associated facial lipodystrophy in HIV-infected patients. *AIDS Patient Care STDS*. Jan 1999;13(1):11-16.

Kiertiburanakul S, Khongnorasat S, Rattanasiri S, Sungkanuparph S. Efficacy of a generic fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR) in Thai HIV-infected patients. *J Med Assoc Thai*. Feb 2007;90(2):237-243.

Kumarasamy N, Solomon S, Chaguturu SK, et al. The safety, tolerability and effectiveness of generic antiretroviral drug regimens for HIV-infected patients in south India. *Aids*. Oct 17 2003;17(15):2267-2269.

Kumarasamy N, Vallabhaneni S, Cecelia AJ, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. *J Acquir Immune Defic Syndr*. Jan 1 2006;41(1):53-58.

Manosuthi W, Athichathanabadi C, Uttayamakul S, Phoorisri T, Sungkanuparph S. Plasma nevirapine levels, adverse events and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole. *BMC Infectious Diseases*. 2007;7:14.

Manosuthi W, Chimsuntorn S, Likanonsakul S, Sungkanuparph S. Safety and efficacy of a generic fixed-dose combination of stavudine, lamivudine and nevirapine antiretroviral therapy between HIV-infected patients with baseline CD4 <50 versus CD4 > or = 50 cells/mm3. *AIDS Res Ther*. 2007;4:6.

Nuesch R, Srasuebkul P, Ananworanich J, Ruxrungtham K, Phanuphak P, Duncombe C. Monitoring the toxicity of antiretroviral therapy in resource limited settings: a prospective clinical trial cohort in Thailand. *J Antimicrob Chemother*. Sep 2006;58(3):637-644.

Paton NI, Earnest A, Ng YM, Karim F, Aboulhab J. Lipodystrophy in a cohort of human immunodeficiency virus-infected Asian patients: prevalence, associated factors, and psychological impact. *Clin Infect Dis*. Nov 15 2002;35(10):1244-1249.

Pujari SN, Dravid A, Naik E, et al. Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. *J Acquir Immune Defic Syndr*. Jun 1 2005;39(2):199-202.

Pujari SN, Patel AK, Naik E, et al. Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. *J Acquir Immune Defic Syndr*. Dec 15 2004;37(5):1566-1569.

Puthanakit T, Oberdorfer A, Akarathum N, et al. Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program. *Clin Infect Dis*. Jul 1 2005;41(1):100-107.
Zhou J, Paton NI, Ditangco R, et al. Experience with the use of a first-line regimen of stavudine, lamivudine and nevirapine in patients in the TREAT Asia HIV Observational Database. *HIV Med*. Jan 2007;8(1):8-16.

Ic. Africa

Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis*. Jul 15 2007;45(2):254-260.
Bourgeois A, Laurent C, Mougnutou R, et al. Field assessment of generic antiretroviral drugs: a prospective cohort study in Cameroon. *Antivir Ther*. 2005;10(2):335-341.
Danel C, Moh R, Anzian A, et al. Tolerance and acceptability of an efavirenz-based regimen in 740 adults (predominantly women) in West Africa. *J Acquir Immune Defic Syndr*. May 2006;42(1):29-35.
Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire. *Aids*. Sep 24 2004;18(14):1905-1913.
Ferradini L, Jeannin A, Pinoges L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. *Lancet*. Apr 22 2006;367(9519):1335-1342.
Forna F, Liechty CA, Solberg P, et al. Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda. *J Acquir Immune Defic Syndr*. Apr 1 2007;44(4):456-462.
Hawkins C, Achenbach C, Fryda W, Ngare D, Murphy R. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. *J Acquir Immune Defic Syndr*. Jul 1 2007;45(3):304-310.
Hosseinipour MC, Corbett AH, Kanyama C, et al. Pharmacokinetic comparison of generic and trade formulations of lamivudine, stavudine and nevirapine in HIV-infected Malawian adults. *Aids*. Jan 2 2007;21(1):59-64.
Kim AA, Wanjiku L, Macharia DK, et al. Adverse Events in HIV-Infected Persons Receiving Antiretroviral Drug Regimens in a Large Urban Slum in Nairobi, Kenya, 2003-2005. *J Int Assoc Physicians AIDS Care (Chic Ill)*. Sep 2007;6(3):206-209.
Laurent C, Diakhate N, Gueye NF, et al. The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study. *Aids*. Jul 5 2002;16(10):1363-1370.
Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet*. Jul 3-9 2004;364(9428):29-34.
Moh R, Danel C, Sorho S, et al. Haematological changes in adults receiving a zidovudine-containing HAART regimen in combination with cotrimoxazole in Cote d'Ivoire. *Antivir Ther*. 2005;10(5):615-624.
Oyugi JH, Byakika-Tusiime J, Ragland K, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *Aids*. May 11 2007;21(8):965-971.
Reddi A, Leeper SC, Grobler AC, et al. Preliminary outcomes of a paediatric highly active antiretroviral therapy cohort from KwaZulu-Natal, South Africa. *BMC Pediatr*. 2007;7:13.
Ssali F, Stohr W, Munderi P, et al. Prevalence, incidence and predictors of severe anaemia with zidovudine-containing regimens in African adults with HIV infection within the DART trial. *Antivir Ther*. 2006;11(6):741-749.
Seyler C, Anglaret X, Dakoury-Dogbo N, et al. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Cote d'Ivoire. *Antivir Ther*. Oct 2003;8(5):385-393.
Sow PS, Otieno LF, Bissagnene E, et al. Implementation of an antiretroviral access program for HIV-1-infected individuals in resource-limited settings: clinical results from 4 African countries. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):262-267.

van Griensven J, De Naeyer L, Mushi T, et al. High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda. *Trans R Soc Trop Med Hyg*. Aug 2007;101(8):793-798.

van Oosterhout JJ, Bodasing N, Kumwenda JJ, et al. Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Trop Med Int Health*. May 2005;10(5):464-470.

Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *Aids*. Jun 26 2006;20(10):1391-1399.

Wamalwa DC, Farquhar C, Obimbo EM, et al. Early response to highly active antiretroviral therapy in HIV-1-infected Kenyan children. *J Acquir Immune Defic Syndr*. Jul 1 2007;45(3):311-317.

Wester CW, Kim S, Bussmann H, et al. Initial response to highly active antiretroviral therapy in HIV-1C-infected adults in a public sector treatment program in Botswana. *J Acquir Immune Defic Syndr*. Nov 1 2005;40(3):336-343.

Wester CW, Okezie OA, Thomas AM, et al. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. *J Acquir Immune Defic Syndr*. Nov 1 2007;46(3):318-322.

II. Review of toxicities reported in treatment of HIV-TB co-infection

IIa. South America

Losso MH, Lourtau LD, Toibaro JJ, Saenz C, Gonzalez C. The use of saquinavir/ritonavir 1000/100 mg twice daily in patients with tuberculosis receiving rifampin. *Antivir Ther*. Dec 2004;9(6):1031-1033.

Pedral-Sampaio DB, Alves CR, Netto EM, Brites C, Oliveira AS, Badaro R. Efficacy and safety of Efavirenz in HIV patients on Rifampin for tuberculosis. *Braz J Infect Dis*. Jun 2004;8(3):211-216.

IIb. Southeast Asia

Patel A, Patel K, Patel J, Shah N, Patel B, Rani S. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naive patients in India who are coinfected with tuberculosis and HIV-1. *J Acquir Immune Defic Syndr*. Sep 1 2004;37(1):1166-1169.

Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Vibhagool A. Initiation of antiretroviral therapy in advanced AIDS with active tuberculosis: clinical experiences from Thailand. *J Infect*. Mar 2006;52(3):188-194.

IIc. Africa

Hoffmann CJ, Charalambous S, Thio CL, et al. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *Aids*. Jun 19 2007;21(10):1301-1308.

Jack C, Lalloo U, Karim QA, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. *J Acquir Immune Defic Syndr*. Aug 1 2004;36(4):929-934.

Srikantiah P, Walusimbi MN, Kayanja HK, et al. Early virological response of zidovudine/lamivudine/abacavir for patients co-infected with HIV and tuberculosis in Uganda. *Aids*. Sep 12 2007;21(14):1972-1974.

III. Review of toxicities for regimens to prevent mother to child transmission

IIIa. South America

Joao EC, Calvet GA, Menezes JA, et al. Nevirapine toxicity in a cohort of HIV-1-infected pregnant women. *Am J Obstet Gynecol*. Jan 2006;194(1):199-202.

Lambert JS, Nogueira SA, Abreu T, et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. *Sex Transm Infect*. Dec 2003;79(6):448-452.

IIIb. Southeast Asia

Phanuphak N, Apornpong T, Teeratakulpisarn S, et al. Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. *HIV Med*. Sep 2007;8(6):357-366.

Read JS, Samuel NM, Parameshwari S, et al. Safety of HIV-1 Perinatal Transmission Prophylaxis With Zidovudine and Nevirapine in Rural South India. *J Int Assoc Physicians AIDS Care (Chic Ill)*. Jun 2007;6(2):125-136.

Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet*. Mar 6 1999;353(9155):773-780.

IIIc. Africa

Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet*. Apr 6 2002;359(9313):1178-1186.

Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*. Sep 4 1999;354(9181):795-802.

Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet*. Sep 13 2003;362(9387):859-868.

Jamisse L, Balkus J, Hitti J, et al. Antiretroviral-associated toxicity among HIV-1-seropositive pregnant women in Mozambique receiving nevirapine-based regimens. *J Acquir Immune Defic Syndr*. Apr 1 2007;44(4):371-376.

Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet*. Mar 6 1999;353(9155):781-785.

SECTION 2

Overview of Studies Assessing Normal Ranges for Laboratory Tests in Various Regions

An exploratory search was conducted to examine what previous work has been presented or published regarding the establishment of normal blood value ranges in various populations. In general, more studies were found examining normal ranges for full blood count values, while fewer studies examined blood chemistry parameters. Most articles focused either on specific hematological variations between populations within the same geographic region, or compared observed normal ranges to accepted standards often derived from Caucasian subjects. Some studies reported general normal ranges or 95% confidence intervals, while others collected separate measurements for males and females. Few studies focused on blood chemistry changes in different age groups. The following tables highlight selective findings of studies that have been conducted in various settings.

AFRICA

Location	Findings	Reference
7 Sites in Africa (Masaka, Entebbe, Kilifi, Kangemi, Kenyatta, Lusaka, Kigali)	Compared to DAIDS toxicity tables, normal ranges often overlapped with 2004 DAIDS grade 1 toxicities	Kamali, 2007
Central African Republic	WBC and hemoglobin ranges lower than reference values; absolute CD4 similar to European ranges; absolute CD8 higher than European ranges; CD4/CD8 ratio lower than European normal ranges	Menard, 2003
East Africa	Differences in hematology compared to Western references, most clinical chemistry measurements agreed with Western normal ranges	De Souza, 2007
Burkina Faso	Lower CD4 in males vs. females; NK higher in males vs. females; absolute CD4 among the highest ever reported in normal range studies from African and Asian populations	Klose, 2007
Ethiopia	WBC and platelet counts lower than adopted reference values (based on non-Ethiopians); absolute CD4 count lower than Dutch references, absolute CD8 higher than Dutch references	Tsegaye, 1999
Ethiopia	Decreased CD4 counts compared to Dutch references; males (Akaki) had higher CD8 counts (not likely due to endemic infection) compared to Dutch or Wonji normal ranges	Kassu, 2001
Uganda	Women with higher mean absolute lymphocyte counts, absolute CD4 counts, CD4/CD8 ratios compared to men; absolute lymphocyte counts lower than North America	Tugume, 1995
Uganda	Significant difference in CD4 cell counts among children compared to Western references ranges (CD4 and CD8 declined until age 18, European/American studies have normal CD4 and CD8 counts for children <10yrs approximately the same as adults); after age 13 higher levels of erythrocyte, hemoglobin, hematocrit, and mean corpuscular volume in males compared to females; gender differences in platelet counts after age 24 (higher in females); after age 18 females had higher CD4 and CD8 compared to men; adults: most hematological indices lower than standard values, eosinophil counts higher than Western ranges; higher CD4 and CD4/CD8 compared to Western normal ranges	Lugada, 2004

MIDDLE EAST

Location	Findings	Reference
Saudi Arabia (men)	Total lymphocyte counts higher than Ethiopian and Dutch normal range studies	Al Qouzi, 2002

EUROPE

Location	Findings	Reference
United Kingdom	Significant differences in platelet count, Hb, RBC, MCHC and HCT observed between genders; reticulocyte reference range lower in males compared to females (not statistically significant), significant difference in coagulation parameters (PT and factor II) between genders	Wakeman, 2007
London (Caucasian, Afrocaribbean, African)	Africans and Afrocaribbeans with lower total WBC, neutrophil and platelet counts compared to Caucasians; counts were lower in Africans than Afrocaribbeans; women with higher neutrophil and platelet counts than men in all ethnic groups	Bain, 1996
Italy	Philippinos with higher mean leucocytes and lymphocytes compared to Italians, especially NK cell ranges	Pasqualetti, 2003
Germany	Increase in absolute peripheral blood CD3/CD4 and CD4/CD8 in females vs. males (up to age 50); NK lower in females vs. males	Jentsch-Ullrich, 2005

NORTH AMERICA

Location	Findings	Reference
USA	Significantly lower hemoglobin levels in African American children compared to white non-Hispanic at all ages (2-18yrs)	Robins, 2007

INDIA

Location	Findings	Reference
Pune	Females with higher absolute WBC, CD4, % CD4 cells, and CD4/CD8 ratio; males higher CD8% and higher CD8 counts (not statistically significant); males with higher hemoglobin vs. females; no variation by age group (18-58+); results similar to Western values; Indian values similar to Caucasian values, but higher than Chinese	Uppal, 2003
Northern India	CD4 lower than global Caucasian populations; Asia and Africa CD4 similar, but different from European population	Amatya, 2004

ASIA

Location	Findings	Reference
Shanghai (Chinese)	Fewer CD4 lymphocytes than Caucasians; slightly lower CD8 lymphocyte subset values compared to Caucasians; no gender difference in CD4	Jiang, 2004

Bibliography

Amatya R, Vajpayee M, Kaushik S, Kanswal S, Pandey RM, Seth P. Lymphocyte immunophenotype reference ranges in healthy Indian adults: implications for management of HIV/AIDS in India. *Clin Immunol*. Sep 2004;112(3):290-295.

Al Qouzi A, Al Salamah A, Al Rasheed R, et al. Immunophenotyping of peripheral blood lymphocytes in Saudi men. *Clin Diagn Lab Immunol*. Mar 2002;9(2):279-281.

Bain BJ. Ethnic and sex differences in the total and differential white cell count and platelet count. *J Clin Pathol*. Aug 1996;49(8):664-666.

De Souza, M. Clinical reference ranges for 3 high altitude sites in east Africa. US Military HIV Research Program. AIDS Vaccine Conference, 2007, Seattle, WA, USA. [PowerPoint presentation].

Jentsch-Ullrich K, Koenigsmann M, Mohren M, Franke A. Lymphocyte subsets' reference ranges in an age- and gender-balanced population of 100 healthy adults--a monocentric German study. *Clin Immunol*. Aug 2005;116(2):192-197.

Jiang W, Kang L, Lu HZ, et al. Normal values for CD4 and CD8 lymphocyte subsets in healthy Chinese adults from Shanghai. *Clin Diagn Lab Immunol*. Jul 2004;11(4):811-813.

Kamali A. Developing local laboratory reference ranges in anticipation of HIV vaccine clinical trials: The experience of seven African sites. IAVI. AIDS Vaccine Conference, Seattle, USA, 20 August, 2007 [PowerPoint presentation].

Kassu A, Tsegaye A, Petros B, et al. Distribution of lymphocyte subsets in healthy human immunodeficiency virus-negative adult Ethiopians from two geographic locales. *Clin Diagn Lab Immunol*. Nov 2001;8(6):1171-1176.

Klose N, Coulibaly B, Tebit DM, et al. Immunohematological reference values for healthy adults in Burkina Faso. *Clin Vaccine Immunol*. Jun 2007;14(6):782-784.

Lugada ES, Mermin J, Kaharuza F, et al. Population-based hematologic and immunologic reference values for a healthy Ugandan population. *Clin Diagn Lab Immunol*. Jan 2004;11(1):29-34.

Menard D, Mandeng MJ, Tothy MB, Kelembho EK, Gresenguet G, Talarmin A. Immunohematological reference ranges for adults from the Central African Republic. *Clin Diagn Lab Immunol*. May 2003;10(3):443-445.

NIH Clinical Center. Historical Reference Ranges. In *Test Guide: Laboratory Medicine, Transfusion Medicine*. Retrieved January 30, 2008, from http://cclnprod.cc.nih.gov/dlm/testguide.nsf/HRRAll?OpenForm&Count=985.

Pasqualetti D, Ghirardini A, Cafolla A, et al. Lymphocyte T subsets and natural killer cells in Italian and Philippino blood donors. *Vox Sang*. Jan 2003;84(1):68-72.

Robins EB, Blum S. Hematologic reference values for African American children and adolescents. *Am J Hematol*. Jul 2007;82(7):611-614.

Tsegaye A, Messele T, Tilahun T, et al. Immunohematological reference ranges for adult Ethiopians. *Clin Diagn Lab Immunol*. May 1999;6(3):410-414.

Tugume SB, Piwowar EM, Lutalo T, et al. Hematological reference ranges among healthy Ugandans. *Clin Diagn Lab Immunol*. Mar 1995;2(2):233-235.

Uppal SS, Verma S, Dhot PS. Normal values of CD4 and CD8 lymphocyte subsets in healthy indian adults and the effects of sex, age, ethnicity, and smoking. *Cytometry B Clin Cytom*. Mar 2003;52(1):32-36.

Wakeman L, Al-Ismail S, Benton A, et al. Robust, routine haematology reference ranges for healthy adults. *Int J Lab Hematol*. Aug 2007;29(4):279-283.

SECTION 3

A. Description of Source Documents

The following sources were used to compile an overview of definitions and severity grading criteria for major adverse events:

SOURCE	FULL TITLE/DESCRIPTION
Dictionary	Dorland's Illustrated Medical Dictionary Accessed online: http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd-a-b-000zPzhtm Stedman's Medical Dictionary, 27th Edition Accessed online: http://www.stedmans.com/section.cfm/45
ACTG Appendix 60	Adult AIDS Clinical Trials Group (ACTG) Diagnoses Appendix Appendix 60 Version 1.1 February 23, 2007
PACTG Appendix 40	Pediatric AIDS Clinical Trials Group (PACTG) Appendix 40 Pediatric/Maternal Diagnoses Version 2.4 11-01-01/10-01-06/12-19-06
ACTG TOX-EG	AACTG Toxicity Evaluation Group (TOX-EG) TOX-EG Definitions 02/21/03
WHO (Adults and Adolescents)	Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. – 2006 rev. WHO 2006.
WHO (Infants and Children)	Antiretroviral therapy for HIV infection in infants and children : towards universal access. Recommendations for a public health aproach. WHO 2006.
DAIDS	Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Publish Date: December, 2004. Version 1.0, 12-28-04
ANRS	Agence Nationale de Recherches sur le SIDA et les hépatites virales B et C (ANRS) ANRS Table For Grading Severity Of Adult Adverse Events Version N°7- November 5th, 2003
TAHOD	TREAT Asia HIV Observational Database (TAHOD) data specifications v2.1 Last updated 22 November 2006
CIOMS	Reporting Adverse Drug Reactions. Definitions of Terms and Criteria for their Use. Council for International Organizations of Medical Sciences (CIOMS), Geneva. 1999.

MedDRA SMQ	Introductory Guide for Standardised MedDRA Queries (SMQs) Version 10.1 MSSO-DI-6226-10.1.0, September 2007 Developed by Council for International Organizations of Medical Sciences (CIOMS)/ MedDRA [Medical Dictionary for Regulatory Activities] Maintenance and Support Services Organization (MSSO)
CTCAE	Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS March 31, 2003 (http://ctep.cancer.gov), Publish Date: August 9, 2006
DMID	Division of Microbiology and Infectious Diseases (DMID) Adult/Pediatric Toxicity Table May 2001
HICDEP	HICDEP: HIV Cohorts Data Exchange Protocol Version 1.2 – 1st of October 2004
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision, Version for 2007 Accessed online: http://www.who.int/classifications/apps/icd/icd10online/

B. List of Common ARV-related Toxicities

The following list of major antiretroviral treatment-related adverse events to be defined was compiled based on initial expert consultations. The terms are listed based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 10.1 classification. This list will be further revised based on meeting discussions and outcomes.

Category **based on MedDRA System Organ Classes [SOC]**	**Major adverse events**
Immune System Disorders	Immune reconstitution syndrome Hypersensitivity (Nevirapine) Hypersensitivity (Abacavir) Severe cutaneous adverse reaction (SCAR) Toxic epidermal necrolysis (TEN) Stevens-Johnson Syndrome (SJS)
Blood and Lymphatic System Disorders	Anemia Neutropenia Agranulocytosis Lymphopenia Thrombocytopenia
Musculoskeletal and Connective Tissues Disorders	Myopathy Rhabdomyolysis Arthralgia Osteopenia Osteonecrosis
Vascular Disorders	Hypotension Hypertension
Respiratory Disorders	Dyspnea Respiratory failure
Skin and Subcutaneous Tissue Disorders	Alopecia Hyperpigmentation Mucocutaneous rash Ingrowing nails Paronychia Pruritis Urticaria
Gastrointestinal Disorders	Acute pancreatitis Diarrhoea Dysphagia Taste disorder Nausea Vomiting
Metabolism and Nutrition Disorders	Dyslipidemia Hypercholesterolemia Hypertriglyceridemia Hyperglycemia Insulin resistance Diabetes mellitus Lipoatrophy Lipohypertrophy Buffalo hump Lactic acidosis Hyperuricemia

Category **based on MedDRA System Organ Classes [SOC]**	**Major adverse events**
Renal and Urinary Disorders	Proteinuria Nephrolithiasis Nephrotic syndrome Renal tubular disorder Renal failure and impairment
Nervous System Disorders	Depression Peripheral neuropathy Parosmia/Smell disorders Dizziness Paresthesia Cerebral hemorrhage Cerebrovascular accident Febrile seizure [pediatric] Neonatal seizure
Cardiac Disorders	Cardiac failure Myocardial Infarction Cardiomyopathy
Investigations	ECG abnormalities
General Disorders and Administration Site Conditions	Chest pain Fatigue Pyrexia Malaise
Hepatobiliary Disorders	Hyperbilirubinemia Hepatitis Jaundice Transaminase levels increased
Psychiatric Disorders	Suicidal ideation Nightmares Abnormal dreams
Reproductive System and Breast Disorders	Gynecomastia Amenorrhea Premature menopause
Neoplasms Benign, Malignant and Unspecified	Non-Hodgkins lymphoma Hodgkin's disease Kaposi's sarcoma CNS lymphoma Anal cancer Cervical cancer Other
Pregnancy, Puerperium and Perinatal Conditions	Pre-eclampsia Eclampsia Spontaneous abortion Intra-uterine death Low birth weight Failure to thrive Premature baby
Congenital Disorders	Congenital anomaly (birth defects)

SECTION 4

Existing definitions and severity grading

Three examples are listed below showing information compiled on existing definitions and severity grading for 1) *anemia,* 2) *lactic acidosis* and 3) *depression,* based on the available sources. A more extensive list of existing definitions will be available at the meeting.

Example 1

Anemia

Definition:
Any condition in which the number of red blood cells per mm^3, the amount of hemoglobin in 100 ml of blood, and/or the volume of packed red blood cells per 100 ml of blood are less than normal; clinically, generally pertaining to the concentration of oxygen-transporting material in a designated volume of blood, in contrast to total quantities as in oligocythemia, oligochromemia, and oligemia. Anemia is frequently manifested by pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.

SOURCE	SEVERITY GRADING			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
ACTG Appendix 60				
PACTG Appendix 40				
ACTG TOX-EG				
WHO (Adults and Adolescents)	8.0 – 9.4 g/dL 4.93 – 5.83 mmol/L	7.0 – 7.9 g/dL 4.31 – 4.92 mmol/L	6.5 – 6.9 g/dL 4.03 – 4.30 mmol/L	<6.5 g/dL <4.03 mmol/L
WHO (Infants and Children)	8.5–10.0 g/dl 1.32–1.55 mmol/l	7.5–<8.5 g/dl 1.16– <1.32mmol/l	6.5–<7.5 g/dl 1.01–<1.16mmol/l	<6.5 g/dl <1.01 mmol/l OR severe clinical symptoms attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy
DAIDS Adult and pediatric ≥ 57 days (HIV positive)	8.5 – 10.0 g/dL 1.32 – 1.55 mmol/L	7.5 – 8.4 g/dL 1.16 – 1.31 mmol/L	6.50 – 7.4 g/dL 1.01 – 1.15 mmol/L	< 6.5 g/dL < 1.01 mmol/L
DAIDS Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL 1.55 – 1.69 mmol/L OR Any decrease 2.5 – 3.4 g/dL 0.39 – 0.53 mmol/L	9.0 – 9.9 g/dL 1.40 – 1.54 mmol/L OR Any decrease 3.5 – 4.4 g/dL 0.54 – 0.68 mmol/L	7.0 – 8.9 g/dL 1.09 – 1.39 mmol/L OR Any decrease ≥ 4.5 g/dL ≥ 0.69 mmol/L	< 7.0 g/dL < 1.09 mmol/L
DAIDS Infant, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL 1.32 – 1.46 mmol/L	7.0 – 8.4 g/dL 1.09 – 1.31 mmol/L	6.0 – 6.9 g/dL 0.93 – 1.08 mmol/L	< 6.00 g/dL < 0.93 mmol/L
DAIDS Infant, 22 – 35 days	9.5 – 10.5 g/dL 1.47 – 1.63 mmol/L	8.0 – 9.4 g/dL 1.24 – 1.46 mmol/L	7.0 – 7.9 g/dL 1.09 – 1.23 mmol/L	< 7.00 g/dL < 1.09 mmol/L

(HIV POSITIVE OR NEGATIVE)				
DAIDS Infant, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL 1.86 – 2.02 mmol/L	10.0 – 11.9 g/dL 1.55 – 1.85 mmol/L	9.0 – 9.9 g/dL 1.40 – 1.54 mmol/L	< 9.0 g/dL < 1.40 mmol/L
ANRS	8.0 – 9.4 g/dL	7.0 – 7.99 g/dL	6.5 – 6.99 g/dL	<6.5 g/dL
TAHOD				
CIOMS	**Preamble** In anaemia the concentration of haemoglobin and volume of packed red blood cells (haematocrit) are less than normal. The normal range of haemoglobin concentration varies with age, sex and altitude; the lower limits are 120g/l in females and 130g/l in males. In validating case reports, established local values should be used. Anaemia can have many causes. It may be genetic or acquired, and the result of diminished production or increased destruction of red cells. Its most common form is hypochromic microcytic anaemia due to iron deficiency from diminished intake of iron, increased demand or chronic blood loss. Vitamin B12 and folate deficiency anaemias are characterized by macrocytosis and megaloblastosis. Anaemia due to increased destruction of red cells is termed *haemolytic anaemia* (see *Anaemia haemolytic*). **Definition** Anaemia is a decrease of the haemoglobin concentration below the normal limits for sex, age and altitude. **Basic requirements for use of the term** Blood-test findings satisfying the definition			
MedDRA SMQ				
CTCAE	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L	<6.5 g/dL <4.0 mmol/L
DMID	9.5 – 10.5 g/dL	8.0 – 9.4 g/L	6.5 – 7.9 g/dL	<6.5 g/dL
HICDEP				
ICD-10				

Example 2

Lactic acidosis

Definition (Dorland's):
A metabolic acidosis occurring as a result of excess lactic acid in the blood, due to conditions causing impaired cellular respiration. It occurs most commonly in disorders in which O2 is inadequately delivered to tissues, e.g., shock, septicemia, or extreme hypoxemia, but it can also result from exogenous or endogenous metabolic defects. Initially manifesting as hyperventilation, it progresses to mental confusion and coma.

ACTG Appendix 60	*Lactic acidosis* As per ACTG TOX-EG definition below
PACTG Appendix 40	**LACTIC ACIDOSIS, SYMPTOMATIC,** new, otherwise unexplained, and persistent occurrence of 1 or more of the following symptoms and a lactate level greater than 1.5 X ULN on at least two separate blood draws. Nausea and vomiting; abdominal pain and gastric discomfort; abdominal distention; increased liver function tests; unexplained fatigue; dyspnea. **LACTIC ACIDOSIS, ASYMPTOMATIC,** defined as hyperlactatemia greater than 1.5 X ULN on two separate blood draws without meeting any of the symptom criteria described above.
ACTG TOX-EG	*Lactic academia/acidosis* ▪ **Definition** Lactate level greater than the upper limit of normal (ULN) confirmed by repeat lactate level analysis may be part of a syndrome referred to as lactic acidemia or lactic acidosis. ▪ Lactic acidemia refers to the presence of plasma lactate above ULN (confirmed) without evidence of a metabolic acidosis. In addition lactic acidemia may be symptomatic or asymptomatic. As lactate levels are highly dependent on collection techniques, careful attention to collection guidelines is necessary and high lactate levels should be repeated for verification. (See "AACTG Venous Lactate Specimen Collection and Storage Guidelines" at http://aactg.s-3.com/member/psmet.htm) ▪ Lactic acidosis is a potentially life-threatening condition and presents with elevated plasma lactate level AND an arterial pH less than 7.35, in general with low bicarbonate or increased anion gap. It is usually accompanied by symptoms which may be vague and/or subtle. ▪ Subcategorization: ▪ Asymptomatic ▪ Symptomatic: New, otherwise unexplained occurrence of one or more of the following symptoms: ▪ Nausea and/or vomiting ▪ Abdominal pain or gastric discomfort ▪ Abdominal distention ▪ Increased hepatic transaminase levels ▪ Unexplained fatigue ▪ Dyspnea ▪ Weight loss ≥ 5% body weight ▪ Muscle weakness ▪ **Disease State Description** ▪ Level A Asymptomatic lactic acidemia < 2 x upper limit of normal (ULN) confirmed by repeat lactate level analysis ▪ Level B: Asymptomatic lactic acidemia ≥ 2 x ULN confirmed by repeat lactate level analysis ▪ Level C: Symptomatic lactic acidemia or lactic acidosis
WHO (Adults and Adolescents)	Lactic acidosis is a rare but severe complication of NRTI therapy caused by mitochondrial dysfunction arising from the inhibition of mitochondrial DNA polymerase by NRTIs.

WHO (Infants and Children)	• Generalized fatigue and weakness • Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) • May have hepatitis or pancreatitis (see above) • Respiratory features (tachypnoea and dyspnoea) • Neurological symptoms (including motor weakness) Laboratory abnormalities: • Increased anion gap • Lactic acidosis • Elevated aminotransferase • Elevated CPK • Elevated LDH
DAIDS	See grading below
ANRS	See grading below
TAHOD	See grading below
CIOMS	
MedDRA SMQ	*Lactic acidosis (SMQ)* • Lactic acidosis is a form of high anion gap metabolic acidosis (fall in blood pH and reduced HCO3 accompanied by a compensatory increase in ventilation (especially Kussmaul respiration) resulting in decreased PCO2 • Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release • Peripheral arterial vasodilatation and central vasoconstriction can be present; the decrease in central and pulmonary vascular compliance predisposes to pulmonary oedema • Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma • Glucose intolerance may occur • Characterized by an increase in plasma L-lactate, which may be secondary to poor tissue perfusion (type A) or to aerobic disorders (type B; includes drugs and toxins) • Acidosis is seldom significant unless blood lactate exceeds 5 mmol/l • Clinical presentation in type B lactic acidosis: - Symptoms listed in order of frequency: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain - Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness (mild confusion to coma; may be accompanied by profound lethargy) - Definitive diagnosis depends on the identification of lactate as the organic anion causing the acidosis
CTCAE	
DMID	
HICDEP	Elevated S-lactate > 2.5 mM (>22.3 mg/dL) AND plasma pH < 7.35 (alternatively: Bicarbonate/ -HCO<= 20 mM (<= 20 meq/L)) AND otherwise unexplained recent onset of at least one of the following: Abdominal distension, anorexia, abdominal pain, nausea, vomiting, diarrhea, increased liver function enzymes, jaundice, dyspnea, fever, neuropathy, generalized weakness, ascending neuromuscular weakness, myalgias, paresthesias, weight loss or hepatomegaly.
ICD-10	

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
ACTG Appendix 60	Level A: Asymptomatic lactic acidemia < 2 x upper limit of normal (ULN) confirmed by repeat lactate level analysis	Level B: Asymptomatic lactic acidemia ≥ 2 x ULN confirmed by repeat lactate level analysis	Level C: Symptomatic lactic acidemia or lactic acidosis	-
PACTG Appendix 40	Asymptomatic/symptomatic, see definition above			
ACTG TOX-EG	Level A: Asymptomatic lactic acidemia < 2 x upper limit of normal	Level B: Asymptomatic lactic acidemia ≥ 2 x ULN confirmed by	Level C: Symptomatic lactic acidemia or lactic acidosis	-

	(ULN) confirmed by repeat lactate level analysis	repeat lactate level analysis		
WHO (Adults and Adolescents)	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life- threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
WHO (Infants and Children)	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
DAIDS	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without lifethreatening consequences	Increased lactate with pH < 7.3 with lifethreatening consequences
ANRS Hyperlactatemia (mmol/l) (collected on venous blood)	2.0 – 2.99*	3.0 – 3.99**	4.0 – 4.99**	≥ 5.0***
TAHOD	-	-	Increased lactate with pH<7.3 without life-threatening consequences	Increased lactate with pH<7.3 with life-threatening consequences
CIOMS				
MedDRA SMQ				
CTCAE				
DMID				
HICDEP				
ICD-10				

Example 3

Depression

Definition (Dorland's):
a mental state of depressed mood characterized by feelings of sadness, despair, and discouragement. Depression ranges from normal feelings of "the blues" through dysthymic disorder to major depressive disorder. It in many ways resembles the grief and mourning that follow bereavement; there are often feelings of low self-esteem, guilt, and self-reproach, withdrawal from interpersonal contact, and somatic symptoms such as eating and sleep disturbances.

ACTG Appendix 60	1. Depression is defined as new onset of depressed mood and/or loss of interest or pleasure for at least 10 out of 14 consecutive days and 2. Five or more of the following symptoms (occurring nearly every day for symptoms 1-5): a. Depressed mood (e.g. sadness, tearfulness) most of the day b. Markedly diminished interest in most activities c. Insomnia or drowsiness d. Psychomotor agitation or retardation e. Feelings of worthlessness or excessive guilt f. Fatigue or loss of energy g. Indecisiveness or diminished concentration h. Recurrent thoughts of death or recurrent suicidal ideation i. Weight loss or gain (5% body weight change in 1 month) Disease state description: Level A: Meets case definition Level B: Symptoms require treatment or interfere with usual activities but not ADLs. Level C: ADLs limited by the mood disorder or hospitalization required Usual activities: All life activities (job, hobbies, social life, etc.) excluding ADLs ADLs: Activities of daily living such as ambulation , bathing, dressing, grooming, feeding and toileting.
PACTG Appendix 40	**POSTPARTUM DEPRESSION,** characterized by symptoms of depression with onset within four weeks after delivery of a child. A fluctuating course and mood lability may be common; severe anxiety, panic attacks, spontaneous crying long after the usual duration of "baby blues" (i.e., 3-7 days postpartum), disinterest in the baby and insomnia may be present.
ACTG TOX-EG	**Depression** New onset of depressed mood and/or loss of interest or pleasure for a 14-day period **AND** Five or more of the following symptoms (occurring nearly every day for symptoms 1-5): 1. Depressed mood (e.g., sadness, tearfulness) most of the day 2. Markedly diminished interest in most activities 3. Insomnia or drowsiness 4. Psychomotor agitation or retardation 5. Feelings of worthlessness or excessive guilt 6. Fatigue or loss of energy 7. Indecisiveness or diminished concentration 8. Recurrent thoughts of death or recurrent suicidal ideation 9. Weight loss or gain (5% body weight change in 1 month) [see grading below]
WHO (Adults and Adolescents)	
WHO (Infants and Children)	
DAIDS	*Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis*), see grading below
ANRS	*Psychiatric,* see grading below

TAHOD	*Depression/anxiety*, see grading below
CIOMS	**Preamble** *Depression* is a term used in everyday language to denote a state of gloom, despondency or sadness. Depression is not necessarily pathological if the decline in mood is appropriate to the circumstances. Mild transient changes in mood should not be confused with medically significant depressive syndromes, which can be severe and life-threatening. **Definition** Depression is a morbid mental state dominated by a lowering of mood and it often includes a variety of associated symptoms, particularly anxiety, agitation, feelings of unworthiness, suicidal ideas, alteration of appetite and sexual function, psychomotor retardation (slowness), sleep disturbance and various somatic symptoms and complaints. **Basic requirements for use of the term** Clinical diagnosis. Organic brain conditions, such as Alzheimer's disease, need to be considered and eliminated.
MedDRA SMQ	*Depression and suicide/self-injury (SMQ)* • Depression is a morbid mental state dominated by a lowering of mood - Often includes a variety of associated symptoms, particularly anxiety, agitation, feelings of unworthiness, suicidal ideas, alteration of appetite and sexual function, psychomotor retardation, sleep disturbance, and various somatic signs and symptoms • Etiology is complex and is thought to reflect changes in brain neurotransmitters, particularly norepinephrine, serotonin, and dopamine • May follow a severe psychosocial stressor • Often associated with chronic medical conditions (such as diabetes, myocardial infarction, carcinomas, stroke) • Associated with a variety of medications (such as antihypertensive drugs, oral contraceptives, and corticosteroids) • Patients also frequently develop other psychiatric conditions, most notable anxiety or panic disorders, and alcohol or substance abuse • Thoughts of death, suicidal ideation, and suicide attempts are frequent complications of depression • Diagnostic criteria as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)© of depression-related disorders include the presence of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day
CTCAE	*Mood alteration - depression*, see grading below
DMID	*Psychiatric*, see grading below
HICDEP	
ICD-10	*Depressive episode* In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe.

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
ACTG Appendix 60	Level A: Meets case definition	Level B: Symptoms require treatment or interfere with usual activities but not ADLs.	Level C: ADLs limited by the mood disorder or hospitalization required	-
PACTG Appendix 40				
ACTG TOX-EG	Level A: Meets case definition	Level B: Symptoms require treatment or interfere with usual	Level C: ADLs limited by the mood disorder OR	-

		activities but not ADLs.	hospitalization required.	
WHO (Adults and Adolescents)				
WHO (Infants and Children)				
DAIDS Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
ANRS Psychiatric	Minor anxiety.	Anxiety or moderate depression. requiring treatment	Major anxiety or identified depression episode requiring treatment	Acute psychosis requiring hospitalization, including suicidal ideas, manic state, hallucinatory delirium.
TAHOD Depression/anxiety	-	-	Alteration in personality-behaviour or in mood that causes inability to perform usual social & functional activities	Behaviour potentially harmful to self or others (eg. Suicidal and homicidal ideation or attempt, acute psychosis) OR causing inability to perform basic self-care functions
CIOMS				
MedDRA SMQ				
CTCAE Mood alteration - depression	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others Grade 5: Death
DMID Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
HICDEP				
ICD-10 *Depressive episode*	**Mild depressive episode.** Two or three of the above symptoms are usually present. The patient is usually	**Moderate depressive episode.** Four or more of the above symptoms are usually present and the patient is likely	**Severe depressive episode without psychotic symptoms.** An episode of depression in which	-

	distressed by these but will probably be able to continue with most activities.	to have great difficulty in continuing with ordinary activities.	several of the above symptoms are marked and distressing, typically loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of "somatic" symptoms are usually present. **Severe depressive episode with psychotic symptoms.** An episode of depression as described in F32.2 [above], but with the presence of hallucinations, delusions, psychomotor retardation, or stupor so severe that ordinary social activities are impossible; there may be danger to life from suicide, dehydration, or starvation. The hallucinations and delusions may or may not be mood-congruent.	