THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al, and the HPTN 052-ACTG Study Team. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis* 2014; published online March 4. http://dx.doi.org/10.1016/S1473-3099(13)70692-3

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HPTN 052 Clinical Manuscript

Analysis Plan

Version 2.0

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Study Overview:

The aim of this analysis is to examine clinical outcomes of immediate versus delayed ART initiation in HPTN 052 in a broader context that reflects a new understanding of overall HIV related morbidity and mortality that may be a consequence of both HIV disease progression, the impact of HIV infection on non-AIDS clinical events as well as adverse events that may be a consequence of treatment. The proposed analyses will describe the frequency and incidence of the clinical events of interest (detailed below) according to immediate versus delayed ART strategy. Survival analysis methods will be used to compare treatment arms and examine associations with covariates of interest with respect to time to first, as well as, all such events. Specific statistical considerations are described in more detail below. ***Changes from Version 1.0 of the analysis plan to this are shown in bold-red-italic face and represent proposed updates to the plan based on baseline data presented to the study team in the preliminary results distributed on May 4th, 2012.***

Study Endpoints

Primary clinical events will be new onset serious clinical events (defined in Table 1.1) with an onset date after the study entry/randomization visit. Secondary analyses will also investigate differences in the incidence of subcategories of these serious targeted events. Specifically, deaths from any cause, AIDS-defining events, tuberculosis, non-AIDS-defining serious clinical events, serious cardiovascular/vascular events, and malignancies (all defined in Table 1.2). Additional secondary analyses will consider an extended list of targeted events that will include all primary clinical events plus additional HIV-associated events and other targeted serious medical conditions (Table 1.2). Throughout, unless otherwise noted in Table 1.1 or Table 1.2 or within analysis plan specifics, repeated events will be included.

Endpoint Capture

With a few exceptions, throughout follow-up in HPTN 052, incident cases of these targeted events were captured in a systematic way on the Index When to Start (IWT-1) case report form (Appendix 1). These CRF then underwent blinded case review by DH & SS and the corresponding events were designated as confirmed/probable/rejected according to ACTG Appendix 60 criteria (February 23, 2007)

(https://www.fstrf.org/apps/cfmx/apps/common/Portal/index.cfm) with additional considerations as given in Table 1.1 and Table 1.2. In preparation for the present analysis, the database was further interrogated for potential targeted events that had previously not been captured on the IWT-1. As part of this process, additional IWT-1 event codes were created for events that were not previously captured in a systematic way on the IWT-1 (specifically, serious liver disease, hepatic transaminitis, end stage renal disease, chronic renal insufficiency, and thrombocytopenia) and sites were queried for input of an IWT-1 CRF for any potential cases highlighted that then underwent case review. More details of this process are provided in Appendix 2.

Unless otherwise noted, qualifying events included in analysis will be those reported on the IWT-1 CRF that were then classified as confirmed or probable by blinded case review by DH and SS. Events reported by sites that were rejected based case review will be excluded. Regardless of the disposition of the case review, repeat events of the following conditions will be also excluded: cirrhosis, esophageal varices, hepatic encephalopathy, hepatic failure, hepatic encephalopathy, congestive heart failure, ESRD, diabetes mellitus, lipodystrophy, dyslipidemia, peripheral neuropathy, and hypertension; repeated events of all other conditions will be included.

Table 1.1: Definition of Primary Clinical Events (Serious Clinical Events)

	Index When to Start (IWT-1) Code[1,2]	**Additional Considerations (over and above ACTG Appendix 60 criteria and IWT-1 code)**
AIDS-defining events		
WHO stage 4	2-16[3], 19-28	
Tuberculosis	17, 18	
Serious bacterial infections	1	
Non-AIDS defining serious clinical events		
Serious liver disease	64	Limited to presence of cirrhosis, esophageal varices, hepatic encephalopathy, hepatic failure or hepatic encephalopathy. *Repeat events will not be included; such events will be queried for reconciliation.*
Serious cardiovascular/vascular disease	56, 57, 58, 59	Limited to myocardial infarction (MI), coronary artery disease (not MI), congestive heart failure and stroke events
End stage renal disease (ESRD)	66	Two consecutive measurements of grade 4 serum creatinine (>3.5xULN) or need for dialysis. *Repeat events will not be included; such events will be queried for reconciliation.*
Non-AIDS malignancy	60	Excluding squamous and basal skin cancer
Diabetes mellitus	50	Incident diagnoses of subjects with evidence of pre-existing diabetes mellitus (diagnosis date) will be excluded. *Repeat events will not be included; such events will be*

[1] Code set for IWT-1 is provided in Appendix 1.

[2] The following new codes have been defined to assist in the review and event definition: (64) Serious Liver Disease; (65) Hepatic Transaminitis; (65) End Stage Renal Disease; (66) Chronic Renal Insufficiency; (68) Thrombocytopenia.

[3] In addition to non-AIDS malignancies, invasive cervical carcinoma (ITS-1, code 4), Kaposi's sarcoma (ITS-1, code 12), and confirmed lymphomas (ITS-1, code 14) endpoints will be included as part of the secondary subcategory of Malignancy.

	Index When to Start (IWT-1) Code[1,2]	**Additional Considerations (over and above ACTG Appendix 60 criteria and IWT-1 code)**
		queried for reconciliation.
Death	Unrelated to other primary clinical event (including deaths related to events found not to meet Appendix 60 endpoint criteria).	

Table 1.2: Definition of HIV-associated and Other Targeted Medical Conditions[1]

	Index When to Start (IWT-1) Code[2,3]	**Additional Considerations (over and above ACTG Appendix 60 criteria and IWT-1 code)**
WHO Stage 2	30-37 (30, 31)[4]	All events reported on IWT-1 will be included without case review. *The following events will be excluded in sensitivity analyses: moderate unexplained weight loss (<10% of bodyweight) (30); recurrent upper respiratory tract infections (31).* ***With the exception of herpes zoster (32), repeat events will not be included; documented resolution of herpes zoster events is required for repeat diagnosis.***
WHO Stage 3	38-44 (39, 40, 41, 44)[4]	All events reported on IWT-1 will be included without case review. *The following events will be excluded in sensitivity analyses: unexplained severe weight loss (>10% of body weight) (39); unexplained chronic diarrhea (40); unexplained persistent fever (41); and unexplained anemia (44).* ***Repeat WHO stage 3 events of unexplained weight loss (39), unexplained chronic diarrhea (40), unexplained fever (41), and persistent oral candidiasis (42) will not be included; only repeat unexplained anemia events occurring after resolution to ≤grade 1 will be included.***
Smear positive malaria	53	***Repeat events occurring <14 days after a resolution of a prior event will not be included.***
Chronic renal insufficiency	67	Per Appendix 60 definition this is defined as serum creatinine 1.0-3.5 x ULN (grade 3) for a period of 3 months or more. ***Repeat events will not be included.***
Hepatic transaminitis	65	2 or more consecutive grade 3 or higher liver function tests (ALT/AST/ALP/total bilirubin) within a 1 year period excluding isolated (i.e. in the absence of other elevated liver enzymes) ATV-associated hyperbilirubinemia. ***Repeat events occurring after resolution to ≤grade1 will be included.***

[1] *Text in the table in bold face reflect changes to the endpoint definitions in relation to repeat events tat were clarified after finalization of Version 1.0 of the protocol but prior to team review of details of the observed data.*

[2] *Code set for IWT-1 is provided in Appendix 1.*

[3] *The following new codes have been defined to assist in the review and event definition: (64) Serious Liver Disease; (65) Hepatic Transaminitis; (65) End Stage Renal Disease; (66) Chronic Renal Insufficiency; (68) Thrombocytopenia.*

[4] *Because of a lack of specificity in diagnostic criteria and thus expected variability in case report of these diagnoses across physicians and sites, sensitivity analyses will be performed with these events excluded.*

	Index When to Start (IWT-1) Code[2,3]	**Additional Considerations (over and above ACTG Appendix 60 criteria and IWT-1 code)**
Lipodystrophy	51[4]	*Repeat events will not be included.*
Dyslipidemia	52	Any grade 3 or higher LDL or total cholesterol; cases will be determined based on a single value. *Repeat events will not be included.*
Peripheral neuropathy	54	Incident diagnoses; diagnoses in subjects with evidence of pre-existing peripheral neuropathy (diagnosis date on or before randomization) will be excluded. *Repeat events will not be included.*
Hypertension	55[4]	Incident diagnoses of subjects with evidence of pre-existing and ongoing hypertension (diagnosis date on or before randomization) will be excluded. *Repeat events will not be included.* ***Note: Further discussion regarding the exclusion of these events in sensitivity analyses took place on 5/29/2012. It was determined that their exclusion was justified since it was unclear that standardized procedures will have been used at the clinics for repeating abnormal BP readings at the time of the clinic visit.***
Lactic acidosis (symptomatic)	63	Symptomatic (level C) Lactic Acidosis. ***Repeat events will not be included.***
Thrombocytopenia	68	Cases will be defined as subjects with 2 or more grade 3 or higher platelet counts (<50,000/mm^3) within a 1 year period. ***Repeat events occurring after resolution to grade ≤1 will be included.***

Analysis Plan

General Analysis Considerations

Analyses will be performed across all regions combined. Where indicated below, sub-group analyses by region (Asia, Africa, Americas) will be performed.

All data to **May 11, 2011** (the day prior to the date of the press release of the HPTN 052 study results) will be used in the analyses.

The two participants enrolled at the Boston site during the run-in period will be excluded from all analyses.

Events will be pooled across disposition (confirmed/probable). All tuberculosis cases (pulmonary/extra-pulmonary) will be grouped as a single event category of Tuberculosis; specific details of each tuberculosis case with respect to organ involvement and mode of diagnosis will be provided as a descriptive listing. Given the lack of discrimination between extra pulmonary and pulmonary tuberculosis, tuberculosis cases will not be counted in event totals for WHO Stage 4 events.

Currently outstanding analyses are shown by highlighted text.

Descriptive Analyses

- Summary statistics (n, %, mean, standard deviation, median, Q1, Q3, minimum and maximum as appropriate) of all covariates measured at or prior to enrollment will be tabulated.

- Subject disposition
  - Subject disposition (see Appendix 3; Table 3.1)
  - Summary of death (Appendix 3; Table 3.2)
  - The proportion of subjects with HIV-1 RNA levels <400 copies/ml over time will be plotted by treatment group across each study week with a 95% confidence interval. Data will be summarized as
    - Intent-to-treat (ITT) with missing data ignored: At each study week the denominator will included all randomized subjects with an HIV-1 RNA level available, the numerator will include all subjects with HIV-1 RNA level <400 copies/ml;
    - ITT with missing data consider failure (HIV-1 RNA>400 copies/ml): At each study week the denominator will included all randomized subjects with potential follow-up to that week (i.e. (5/11/2012 – PPT randomization date)/7 >week); the numerator will include all subjects with HIV-1 RNA level <400 copies/ml.
  - The median (Q1, Q3) CD4 cell count will be plotted by treatment group across each study week. Again, data will be summarized as ITT assuming that missing data can be ignored, i.e. at each study week including all randomized subjects with a CD4 measurement available.
  - The time to ART initiation in the delayed treatment group will be plotted using the method of Kaplan-Meier; the median time to ART initiation will be estimated with 95% confidence interval.
  - Sub-group analyses by region (Asia, Africa, Americas) will be performed.

- In order to understand prophylaxis use over time and by treatment arm
  - The proportion of subjects taking a) INH and b) Septra for prophylaxis will be plotted by study visit by arm.
  - The time to first initiation of a) INH and b) cotrimoxazole (TMP/Sulfa) for prophylaxis with be plotted

using the method of Kaplan-Meier with an accompanying life-table providing the numbers of subjects and probability of first initiation at 24 week intervals.
Note: The determination of INH and TMP/Sulfa use as for prophylaxis will be made based on the recorded indication on the ICM-1 CRF, lack of associated AE, and, (for TMP/Sulfa only) duration of use of >21 days.

- Sub-group analyses by region (Asia, Africa, Americas) will be performed.

Primary Analyses

- The incidence of primary clinical events will be estimated by arm (with 95% confidence intervals)
  - The same summaries for the following pre-defined subcategories of primary clinical events (death, AIDS-defining events, Tuberculosis, non-AIDS-defining serious clinical events, serious cardiovascular/vascular events, and malignancies) will also be provided.
  - To accommodate multiple events per individual, Poisson regression with robust standard errors will be used for confidence interval estimation on the overall incidence and treatment group comparisons.
  - Mock table provided in Appendix 3; Table 3.3 ***(Table 5.2 of the preliminary analysis report)***.
  - Sub-group analyses by region (Asia, Africa, Americas) will be performed.
    Note: Analyses by region will include one table of estimated event incidence by treatment group for each region.

- Descriptive summaries of primary clinical events by treatment arm
  - Number (%) of subjects experiencing at least one of each of the primary clinical events
    - Mock table provided in Appendix 3; Table 3.4 ***(Table 5.1 of the preliminary analysis report)***.
  - Distribution of HIV-1 RNA level and CD4 cell counts at the time of clinical event
    - Mock table provided in Appendix 3; Table 3.5.
    - Mock Figure provided in Appendix 3; Figure 3.1.
  - Sub-group analyses by region (Asia, Africa, Americas) will be performed.
    Note: Summaries of events by region will not be presented by treatment group, rather the descriptive summary will present types of events by region (i.e. As Table 5.1 with column as regions instead of treatment group).
    Notes:
    - *This will be the only analysis in which details of individuals events will be provided.*
    - *Deaths associated with specific clinical events will be counted for the specific event.*

- Descriptive summaries of tuberculosis events
  - Appendix 3; Table 3.6.

- The distribution of time to first primary clinical event will be estimated by treatment arm using the method of Kaplan-Meier;
  - Time will be measured from randomization to the diagnosis of first qualifying clinical event.
  - Subjects not experiencing a primary clinical event prior to May 11, 2011 will be censored on that date.
  - Subgroup analyses by region, sex and baseline CD4 cell count (<350; 350-499; >500) will be performed.

- The distribution of time to first event will be estimated by treatment arm for each pre-defined subcategory of primary clinical events (death, AIDS-defining events, Tuberculosis, non-AIDS-defining serious clinical

events, serious cardiovascular/vascular events, and malignancies) using the method of Kaplan-Meier.

- Time will be measured from randomization to the diagnosis of first qualifying clinical event.
- Subjects not experiencing an event prior to May 11, 2011 will be censored on that date.

  Note: Subgroup analyses by region, sex and baseline CD4 cell count (<350; 350-499; >500) will NOT be performed.

- ***The cumulative incidence of first event will be estimated over time by treatment arm for each pre-defined subcategory of primary clinical events (AIDS-defining events, Tuberculosis, non-AIDS-defining serious clinical events, serious cardiovascular/vascular events, and malignancies). Methods for competing risk will be used treated deaths from other causes as a competing risk.***
  - ***Time will be measured from randomization to the diagnosis of first qualifying clinical event or death from other causes whichever occurs first.***
  - ***Subjects not experiencing an event prior to May 11, 2011 will be censored on that date.***

    Note: Subgroup analyses by region, sex and baseline CD4 cell count (<350; 350-499; >500) will NOT be performed.

    Note: Given the relatively small number of deaths, the more appropriate handling of censoring due to death in these analyses not expected to differ dramatically from the Kaplan-Meier analyses. These analyses will therefore be of the lowest priority and may not be distributed at the same time as the remainder of the analyses.

- The impact of immediate versus delayed ART for primary clinical events (as expressed by a relative hazard) will be evaluated using Cox proportional hazards regression stratified by region; since this is a randomized comparison, no adjustment for covariates will be made.

- Factors associated with hazard of primary clinical events will be evaluated using Cox proportional hazards regression stratified by region. The primary analysis will consider only covariates evaluated at or prior to enrollment. Secondary models will evaluate associations with time updated health status information and prophylaxis use.

  Note: A treatment effect will not be included in any of the analyses including time-updated covariates since its interpretation is unclear in the presence of time-updated covariates that are known to be influence by the strategy itself.

  Close attention to diagnostic tests for the basic proportionality assumptions with respect to covariates and to linearity assumptions of continuous covariates. Interactions of the treatment effect and key pre-treatment covariates (highlighted below) will be evaluated with by the presentation of subgroup specific unadjusted hazards ratio in a forest plot and tests for interaction in the context of an adjusted Cox proportional hazards model.
  - <u>Covariates of interest</u>

    Covariates will be modeled as continuous unless otherwise noted; categories may be collapsed based on category size. ***Categorical variables that cannot be collapsed to provide all cell sizes having at least 50 individuals in each category will be excluded (see below for proposed collapsing of categories and exclusions based on baseline data presented to date).***
    - Randomized ART strategy
    - Demographic and enrollment information
      - Age (<25; 25-39; 40+ years)

- Sex (Male; Female) – *interaction with treatment effect*
- Region (Asia; Africa; Americas) –*interaction with treatment effect*

▪ Enrollment Health Status Information
- HIV-1 RNA level - *interaction with treatment effect*
- CD4 cell count – *interaction with treatment effect*
- Body mass Index (<18; 18-25; 25-30; >30 kg/m^2)
- ALT(by grade: 0; 1; 2+) (<1.25; 1.25-2.5; ≥2.6 x ULN); *ALT≤ 5xULN required for entry*
  - ***Given the small number of subjects with grade 2 ALT at baseline, ALT will not be included in modeling. In discussion on 5/29/2012, exclusion was preferred over a binary variable grade 0 versus grade 1+ since grade 1 ALT were not felt to be helpful.***
- Serum creatinine (by grade: 0; 1 2+) (≤1; 1.1-1.3; ≥1.4 x ULN) ; Cal CrCl≥*60mL/min required for entry*
- Hemoglobin (by grade: 0; 1; 2+); *Note: Hgb≥ 7.5g/dL required for entry*
  - ***Based on observed baseline data, grade 1, 2+ will be combined to give a binary variable grade 0 or 1+.***

▪ Pre-existing conditions
- Hepatitis B (Yes; No) ***(N=91)***
- ~~**Hepatitis C (Yes; No)**~~
- Peripheral neuropathy (Yes; No)
  - ***Will not be included based on observed baseline prevalence (N=13).***
- Diabetes (Yes; No)
  - ***Will not be included based on observed baseline prevalence (N=8).***
- Hypertension (Yes; No) ***(N=90)***
- Active Tuberculosis at study entry (Yes; No) ***(N=43)***
- Prior history of tuberculosis (Yes; No) ***(N=37)***
  - ***Final determination of whether active TB or a prior history of TB will not be included in analyses is pending review of the active TB cases (by BG). Per study entry criteria these should be cases ongoing at study entry for which intensive treatment had been completed.***

▪ Enrollment prophylaxis use (Initiated at or prior to randomization)
- INH (Yes; No)
  - ***Based on baseline prevalence (N=12), will not be included based on observed baseline prevalence.***
- Septra prophylaxis (Yes; No) ***(N=199)***
  - ***As defined by Septra use at study initiation in Preliminary analyses.***

▪ Time-updated health status and prophylaxis use
- HIV-1 RNA level
- CD4 cell count
- INH (Yes; No)
- Septra prophylaxis (Yes; No)

Note: These analyses are going to be pretty hard to interpret and we will leave to the lowest priority.

- To complement these analyses Andersen-Gill proportional hazards models will also be used to evaluate repeated events.

Note: These analyses are considered of lower priority and may not be performed until after the

distribution of the remainder of analyses.

Secondary Analyses

Analyses of all targeted clinical events (any of the events listed in Tables 1.1 and Table 1.2 combined) will be performed as follows.

- Descriptive summaries of the number (%) of subjects experiencing at least one targeted clinical event will be provided.
  - Mock table provided in Appendix 3; Table 3.7.
  - Sub-group analyses by region (Asia, Africa, Americas) will be performed.
    As for the complimentary table of primary events, these data will not be presented by treatment group. i.e. one Table of a similar structure to Table 5.3 of the preliminary analysis report will be presented with region as the columns.
    Notes:
    - *This will be the only analysis in which details of individuals events will be provided.*
    - *Deaths associated with specific clinical events will be counted for the specific event.*

- The incidence of all targeted clinical events will be estimated by arm (with 95% confidence intervals)
  - Because of a lack of specificity in diagnostic criteria and thus expected variability in case report of these diagnoses across physicians and sites, sensitivity analyses will be performed with select events (noted in Table 1.2) excluded.
  - To accommodate multiple events per individual, Poisson regression with robust standard errors will be used for confidence interval estimation on the overall incidence and treatment group comparisons.
  - See Mock table provided in Appendix 3; Table 3.3.

- The distribution of time to first targeted event will be estimated by treatment arm using the method of Kaplan-Meier.
  - Time will be measured from randomization to the diagnosis of first qualifying clinical event.
  - Subjects not experiencing an event prior to May 11, 2011 will be censored on that date.
    Note: Subgroup analyses by region, sex and baseline CD4 cell count (<350; 350-499; >500) will NOT be performed.

- The relative hazard of immediate versus delayed ART for all targeted clinical events will be evaluated using Cox proportional hazards regression stratified by region; since this is a randomized comparison, no adjustment for covariates will be made.

- Factors associated with hazard of targeted clinical events will be evaluated using Cox proportional hazards regression stratified by region using the same covariates and modeling strategy as outlined for the primary analyses.

Note: Andersen-Gill analyses including repeated events will be performed. However, these analyses are considered of lower priority and may not be performed until after the distribution of the remainder of analyses.

Appendix 1 Index When to Start (IWT-1) Case Report Form

The IWT-1 was designed to capture specific details of targeted clinical events including diagnostic criteria that contributed to the diagnosis - including contributing signs & symptoms, laboratory and diagnostic evaluations and response to treatment (not limited to ART). Information captured on the IWT-1 forms the basis for blinded chair review of targeted clinical events.

A1.1 IWT-1 Code set

Index When to Start (IWT-1)

The Index When to Start CRF collects data on HIV/AIDS-related illnesses, WHO Stage 2 and 3 Clinical Events, and other targeted conditions, according to LOA #1 to version 3.0 of the protocol. Fax the form within 3 weeks of first becoming aware of the event.

Events listed in Appendix IV as HIV/AIDS-related illnesses (codes 01–28) and Other Targeted Medical Conditions (codes 50–63) require completion of all pages of the CRF. All other events (codes 30–44) require completion of page 1 only.

Event Number: Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Index When to Start pages after faxing, unless instructed by SCHARP.

Item 1 Diagnosis Code: Refer to the Code Lists below. If a diagnosis is later found to be incorrect, draw a line through the diagnosis code and record the correct code.

HIV/AIDS-related Illnesses (WHO Stage 4, severe bacterial infections and pulmonary TB) **Code List**

01	Bacterial infections, severe (WHO Stage 3) (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)	11	Isosporiasis, chronic intestinal (> 1 month duration) (confirmatory diagnostic testing required)	21	Mycosis, disseminated, coccidiomycosis
02	Bacterial pneumonia, recurrent, severe (≥ 2 episodes in 12 months)	12	Kaposi's sarcoma	22	Penicilliosis, disseminated
03	Oesophageal candidiasis (or candidiasis of bronchi, trachea, or lungs)	13	Leishmaniasis, atypical, disseminated	23	Pneumocystis pneumonia
04	Cervical carcinoma, invasive, confirmed by biopsy	14	Lymphoma, Burkitt, immunoblastic, primary central nervous system/ cerebral, B cell non Hodgkin (confirmatory diagnostic testing required)	24	Progressive multifocal leukoencephalopathy (PML)
05	Chagas' disease	15	*Mycobacterium avium* complex (MAC)	25	Septicemia, recurrent, including non-typhoidal *Salmonella*
06	Cryptococcosis, extrapulmonary including meningitis	16	*M. kansasii*, disseminated or extrapulmonary	26	Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy
07	Cryptosporidiosis, chronic intestinal (> 1 month duration)	17	*Mycobacterium tuberculosis*, pulmonary (WHO Stage 3)	27	Toxoplasmosis of brain/central nervous system
08	Cytomegalovirus disease (retinitis or infection of other organs)	18	*Mycobacterium tuberculosis*, extrapulmonary	28	Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥ 2 loose stools per day ≥ 1 month) or chronic weakness and documented fever ≥ 1 month (MAC)
09	Encephalopathy, HIV-related	19	Mycobacterial infection, other species or unidentified species, disseminated or extrapulmonary		
10	Herpes simplex, chronic (orolabial, genital, or anorectal site, > 1 month duration), or bronchitis, pneumonitis, esophagitis, or visceral at any site	20	Mycosis, disseminated, extrapulmonary histoplasmosis		

WHO Stage 2 and 3 Clinical Events Code List (excluding pulmonary TB and severe bacterial infections; see HIV/AIDS-related Illnesses Code List above)

Stage 2		34	Oral ulcerations, recurrent	39	Unexplained severe weight loss (> 10% body weight)
30	Moderate, unexplained weight loss (< 10% body weight)	35	Papular puritic eruptions	40	Unexplained chronic diarrhea
31	Upper respiratory tract infections, recurrent (sinusitis, tonsillitis, otitis media and pharnygitis)	36	Seborrhoeic dermatitis	41	Unexplained persistent fever
32	Herpes zoster	37	Fungal nail infections	42	Oral candidiasis, persistent
33	Angular cheilitis	**Stage 3**		43	Oral hairy leukoplakia
		38	Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis	44	Unexplained anemia

Other Targeted Medical Conditions Code List

50	Diabetes mellitus	56	Myocardial infarction	60	Malignancy, newly diagnosed, excluding squamous cell and basal cell cancer of the skin
51	Lipodystrophy	57	Coronary artery disease, not myocardial infarction	61	Renal insufficiency
52	Dyslipidemia	58	Congestive heart failure, not HIV cardiomyopathy	62	Liver disease
53	Malaria	59	Stroke	63	Lactic acidosis
54	Sensory peripheral neuropathy				
55	Hypertension				

Item 1d: Record the visit code at which the event or illness was first reported.

Item 1f: Recurrent is defined as an event that recurs after it has clinically resolved after treatment.

Item 1g: Date event started is the date on which issues or symptoms related to the event started. At minimum, month and year are required.

Item 1h: Date of diagnosis is the date on which the confirmed or probable diagnosis was made. If a diagnosis is later found to be incorrect, draw a line through the diagnosis date and record the date of the correct diagnosis.

Item 1i: At the participant's Termination visit, the "Resolved" box must be marked and the date recorded for each event or illness OR the "Continuing at end of study participation" box must be marked.

Version 1.0, 24-JAN-08
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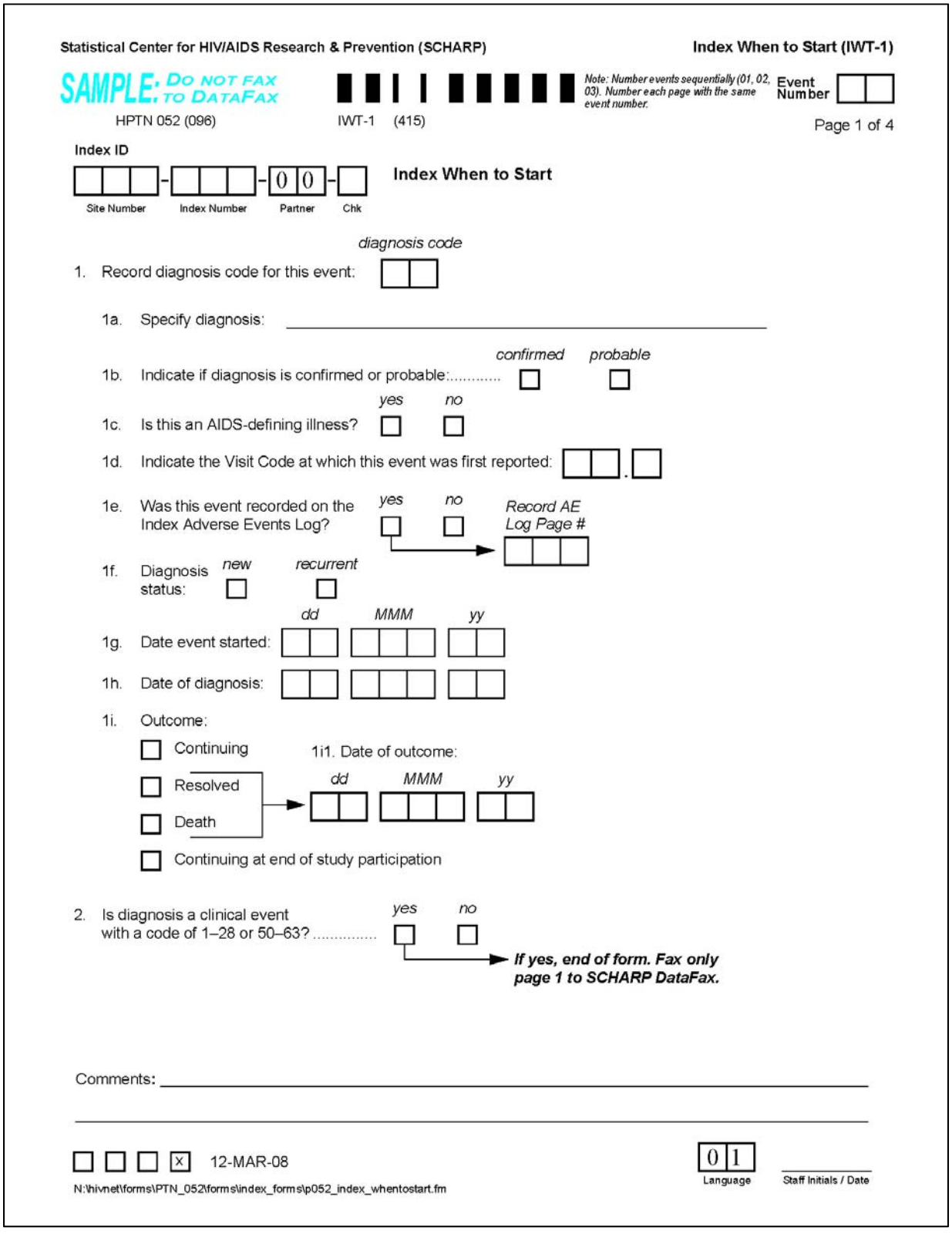
A1.2 IWT-1 Data Entry Pages



Statistical Center for HIV/AIDS Research & Prevention (SCHARP)

Index When to Start (IWT-1)

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number events sequentially (01, 02, 03). Number each page with the same event number.

Event Number

HPTN 052 (096) IWT-1 (415)

Page 1 of 4

Index ID

Site Number - Index Number - Partner (0 0) - Chk

Index When to Start

1. Record diagnosis code for this event: (diagnosis code)

1a. Specify diagnosis: _____

1b. Indicate if diagnosis is confirmed or probable:..... confirmed ☐ probable ☐

1c. Is this an AIDS-defining illness? yes ☐ no ☐

1d. Indicate the Visit Code at which this event was first reported: ☐☐.☐

1e. Was this event recorded on the Index Adverse Events Log? yes ☐ no ☐ → Record AE Log Page # ☐☐☐

1f. Diagnosis status: new ☐ recurrent ☐

1g. Date event started: dd ☐☐ MMM ☐☐☐ yy ☐☐

1h. Date of diagnosis: dd ☐☐ MMM ☐☐☐ yy ☐☐

1i. Outcome:

☐ Continuing

☐ Resolved

☐ Death

→ 1i1. Date of outcome: dd ☐☐ MMM ☐☐☐ yy ☐☐

☐ Continuing at end of study participation

2. Is diagnosis a clinical event with a code of 1–28 or 50–63? ..... yes ☐ no ☐

→ ***If yes, end of form. Fax only page 1 to SCHARP DataFax.***

Comments: _____

☐☐☐☒ 12-MAR-08

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01 Language

_____ Staff Initials / Date

Statistical Center for HIV/AIDS Research & Prevention (SCHARP) **Index When to Start (IWT-2)**

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number events sequentially (01, 02, 03). Number each page with the same event number. Event Number

HPTN 052 (096) IWT-2 (416) Page 2 of 4

Index ID

Site Number - Index Number - Partner (0 0) - Chk

Index When to Start

Diagnosis Code

3. Complete the information below for each abnormal laboratory result that supports or confirms the diagnosis.

OR ☐ No laboratory results to report. → ***Go to item 4.***

	Test Code	Date Specimen Obtained (dd MMM yy)	Laboratory Value	Units Code
3a.				
3b.				
3c.				
3d.				
3e.				
3f.				

4. Were any other diagnostic tests used to establish/ confirm this diagnosis? ..... yes ☐ no ☐

→ ***If yes, go to item 4b.***

4a. If no, how was the diagnosis made?

Specify: _____

_____

→ ***Go to item 5.***

☐ ☐ ☐ ☒ 12-MAR-08

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01 Language

Staff Initials / Date

Statistical Center for HIV/AIDS Research & Prevention (SCHARP) **Index When to Start (IWT-3)**

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number events sequentially (01, 02, 03). Number each page with the same event number. Event Number

HPTN 052 (096) IWT-3 (417) Page 3 of 4

Index ID

Site Number - Index Number - Partner (0 0) - Chk

Index When to Start

Diagnosis Code

Complete the information below for each test. For diagnoses of tuberculosis, list all diagnostic tests regardless of result.

	Test Type	Result Code	Date Specimen Obtained/Test Done (dd-MMM-yy)	Specify Test, Site, Units	Specify Result
4b.					
4c.					
4d.					
4e.					
4f.					
4g.					

5. Was the index receiving any antiretroviral or other medications at the time of this diagnosis which are known or suspected to be related to the event?..... yes ☐ no ☐ → ***If no, go to item 6.***

Complete the information below for each medication.

	Drug Code	Relationship of diagnosis to Medication/Treatment *Mark only one.*	Action Taken with Medication *Mark only one.*
5a.	specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued
5b.	specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued

☐ ☐ ☐ ☒ 12-MAR-08

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Statistical Center for HIV/AIDS Research & Prevention (SCHARP) — **Index When to Start (IWT-4)**

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number events sequentially (01, 02, 03). Number each page with the same event number. Event Number ☐☐

HPTN 052 (096) IWT-4 (418) Page 4 of 4

Index ID

☐☐☐-☐☐☐-0 0-☐ (Site Number - Index Number - Partner - Chk)

Index When to Start

Diagnosis Code ☐☐

	Drug Code	Relationship of diagnosis to Medication/Treatment *Mark only one.*	Action Taken with Medication *Mark only one.*
5c.	☐☐☐☐☐☐☐☐ specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued
5d.	☐☐☐☐☐☐☐☐ specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued

6. Were specific treatments recommended or initiated to treat this diagnosis? ..... *yes* ☐ *no* ☐ → ***If no, go to item 7.***

6a. If yes, did this lead to an improvement in the condition? ..... *yes* ☐ *no* ☐

Complete the information below for each therapy.

	Drug Code	Specify
6a1.	☐☐☐☐☐☐☐☐	
6a2.	☐☐☐☐☐☐☐☐	
6a3.	☐☐☐☐☐☐☐☐	
6a4.	☐☐☐☐☐☐☐☐	
6a5.	☐☐☐☐☐☐☐☐	
6a6.	List any other treatments recommended, e.g. diet, exercise:	

7. Was any other information used to arrive at this diagnosis? *yes* ☐ *no* ☐ → ***If no, end of form.***

7a. If yes, specify: _____

☐☐☐☒ 12-MAR-08

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01 Language _____ Staff Initials / Date

Appendix 2 Operational procedures for Event Identification

General Operational Considerations

- Events recorded on the IWT-1 form that occurred prior to February 12, 2011 have been reviewed by DH and SS. Unless there are additional criteria needed to make case definitions, these previously reviewed and accepted events will not be re-reviewed.
- Events recorded on the IWT-1 form with onset date between February 12, 2011 and May 11, 2011 will be reviewed by DH and SS.
- Maija Andersen (SCHARP Clinical Affairs) working with Atlas to move IWT-1events into "Awaiting Further Review' bin for SS & DH
- Unless there are additional criteria needed to make case definitions, previously reviewed and accepted events will not be re-reviewed
- The following new codes will be defined to assist in the review and event definition: (64) Serious Liver Disease; (65) Hepatic Transaminitis; (65) End Stage Renal Disease; (66) Chronic Renal Insufficiency; (68) Thrombocytopenia.
- In many instances, the case identification procedures outlined below cast a broad net to highlight potential events; final determination regarding confirmed/probable/rejected events will be made based on Appendix 60 definitions and additional criteria as outline in Table 1 and Table 2 during case review by SS & DH.
- Repeat cases of the same diagnosis will be reviewed in order to confirm multiple events (as opposed from continuing/worsening prior cases). Given the nature of the events, repeat cases of cirrhosis, esophageal varices, hepatic encephalopathy, hepatic failure, hepatic encephalopathy, ESRD, diabetes mellitus are not expected; any identified cases will be identified and reconciled appropriately. For the following conditions, in the event of any confirmed/probable repeat cases remaining in the database after review only the first event will be retained for analysis.

Table 2.1: Operational criteria for identifying and reviewing events for inclusion

	IWT-1 Code	SCHARP & DH, SS operational procedures for identifying potential cases for review
Death		AEs Grade 5 AEs/Death will be queried for an IWT-1 form, as applicable. *Note: Deaths do not need to have an IWT-1form. Rather, deaths associated with a potentially qualifying primary or secondary event should be reported as the outcome of that primary/secondary event. These queries are to ensure that all appropriate IWT-1 forms have been captured.*
WHO stage 4	2-16, 19-28	
Tuberculosis	17, 18	• To ensure that all TB diagnoses are new diagnoses a listing of PPT's with 17 or 18 IWT-1and see if Pre-Existing TB on PEC form • Cases with pre-existing TB will be reviewed by DH &SS to confirm that they are likely separate events
Serious bacterial infections	1	• A listing of all unique preferred terms used for AEs in *Investigations & Infestations* SOC will be reviewed by DH & SS; sites • Maija (SCHARP Clinical Affairs) will query sites for IWT-1 forms for selected terms • Submitted IWT-1 forms will be submitted for review by DH & SS

	IWT-1 Code	SCHARP & DH, SS operational procedures for identifying potential cases for review
Serious liver disease limited to cirrhosis, varices, hepatic failure, and encephalopathy	64	• A new IWT-1 code 64 for Serious Liver Disease is defined • SS & DH will review unique preferred terms for AEs recorded under *Hepatobiliary SOC & GI Disorders* SOCs terms that may indicate Serious Liver Disease events • Statisticians will generate a listing of subjects with evidence of two or more grade 4 AST & ALT laboratory values • Maija will query sites for new IWT-1 with code 64 for individuals with AEs for the identified preferred terms and those identified on the lab listings • SS & DH will review all subsequently submitted IWT-1code 64 events for qualifying serious liver disease events • Listing of PPT's with 64 IWT-1to rule out pre-existing Hepatitis B or C on PEC form Note: Existing IWT-1code 62 (liver disease) endpoints will not be used for primary endpoint determination
Cardiovascular disease limited to MI, coronary artery disease (not MI), and congestive heart failure	56, 57, 58	• AEs reported in the *Cardiac Disorders* SOC to be reviewed by Maija for preferred terms & query selected AEs for appropriate IWT-1 • Submitted IWT-1 forms will be submitted for review by DH & SS
End stage renal disease (ESRD)	66	• Events occurred by February 12, 2011 have been reviewed by DH and SS. • New IWT-1code 66 For 'End Stage Renal Disease (ESRD)' • Maija will review a listing of AEs using unique preferred terms in the *Renal* SOC • Subjects with current IWT-1 code 61 events (renal insufficiency) will be reviewed for subjects on dialysis • Statisticians will generate listing of subjects experiencing two consecutive measurements of grade 4 serum creatinine (>3.5xULN) • Sites will be queried by Maija for IWT-1 with new code 66 for any cases highlighted above • Submitted IWT-1 forms will be submitted for review by DH & SS
Cerebrovascular disease (stroke)	59	• AEs in *Nervous System Disorders* SOC to be reviewed by Maija for preferred terms & query selected AEs for IWT-1 • Submitted IWT-1 forms will be submitted for review by DH & SS
Malignancy (excluding squamous and basal skin cancer)	60	• Selected (from SS & DH on call) AEs in *Neoplasms* SOC to be query for IWT-1by Maija • Submitted IWT-1 forms will be submitted for review by DH & SS
Diabetes mellitus	50	• Selected AEs in *Metabolism & Nutrition* SOC to be queried for IWT-1(DM, diabetic ketoacidosis, Grade 4 elevated blood glucose) • Submitted IWT-1 forms will be submitted for review by DH & SS
WHO Stage 2 or 3	30-44	• All events reported on IWT-1 will be included without case review; no additional query of the AE database for these events will be made as uniform reporting of such events as AEs was not required per protocol. The following events will be excluded in sensitivity analyses: • Maija to only query exact match AE to WHO stage 2 or 3 terms for IWT-1(ex. Herpes zoster, PPE, seb derm …)

	IWT-1 Code	SCHARP & DH, SS operational procedures for identifying potential cases for review
Smear positive malaria	53	• Maija query selected Malaria AEs (that are not 'clinical diagnosis' or are marked as Confirmed as 'smear positive' on AE) for WTS • Submitted IWT-1 forms will be submitted for review by DH & SS
Chronic renal insufficiency	67	• Listing of two or more consecutive measurements of serum creatinine 1.0-3.5 x ULN (grade 3) for 3 months or more • Maija to query site for ppt's who meet this lab criteria to submit new diagnosis code 67 • Submitted IWT-1 forms will be submitted for review by DH & SS
Hepatic transaminitis	65	• Listing of Grade 3 or higher AST/AST/ALP/bilirubin • Maija to query site for IWT-1for PPTS meeting lab criteria for new code 65 • SS & DH are not using IWT-1 code 62 for secondary endpoint determination • Submitted IWT-1 forms will be submitted for review by DH & SS
Lipodystrophy*	51	• Maija to query AE for lipodystrophy for WTS • Sites will be queried for an IWT-1 forms for identified cases • Submitted IWT-1 forms will be submitted for review by DH & SS
Dyslipidemia	52	• Maija to query grade 3 AEs for IWT-1: LDL Cholesterol, total Cholesterol, hypertriglyceridemia; Elevated Triglycerides (Investigations SOC & Metabolism & Nutrition SOC) • Submitted IWT-1 forms will be submitted for review by DH & SS
Peripheral neuropathy	54	• Maija to query AEs in Nervous Systems SOC for peripheral neuropathy for WTS • Listing of ppts with Code 54 IWT-1and PEC of Peripheral neuropathy • Submitted IWT-1 forms will be submitted for review by DH & SS
Hypertension	55	• Vascular Disorders SOC: AEs for HTN • Listing of ppts with Code 55 IWT-1and PEC of Hypertension • Maija will query sites for IWT-1 forms for identified cases • Submitted IWT-1 forms will be submitted for review by DH & SS
Lactic acidosis (symptomatic)	63	• Events occurred by February 12 have been reviewed by DH and SS. • AE data will be queried of preferred terms hyperlactacidemia and lactic acidosis 'symptomatic' for WTS • Lab data will be queried for 2 consecutive grade 2 or higher lactate levels over a 3 month period • Maija query sites for IWT-1 • Submitted IWT-1 forms will be submitted for review by DH & SS
Thrombocytopenia	New Code 68	• Lab data will be queried for 2 consecutive grade 3 or higher platelet counts (<50,000/mm^3) within a 1 year period • Maija will query sites for IWT-1 for identified cases • Submitted IWT-1 forms will be submitted for review by DH & SS

Appendix 3 Proposed Table Format

Table 3.1: Subject Disposition

		Treatment group		
		Delayed	**Immediate**	
		N (%)	**N (%)**	**Total**
Number randomized		877	886	1763
Number in follow-up on May 11th, 2011		Xxx (XX%)		
Number discontinued follow-up prior to May 11th, 2011		Xxx (XX%)		
Reasons for study discontinuation				
	Death	XXX		
	Lost to follow-up	XXX		
	Withdrew consent	XXX		
	….			
Duration of follow-up achieved (weeks)[1]	Median			
	10%-90%			
	Min-Max			
Number of subjects initiating ART		183 (21%)	886 (100%)	

[1] *Weeks from study entry to last visit on study*

Table 3.2: Causes of Death

	Treatment Group		
	Delayed	**Immediate**	
	N (%)	**N (%)**	**Total**
All deaths	**XXX (XX%)**	**XXX (X%)**	**XX (XX%)**
Causes of death			
Tuberculosis	n	n	
Myocardial infarction	**n**	**n**	
End stage renal disease	**n**	**n**	
Cerebrovascular disease (stroke)	**n**	**n**	
Serious bacterial infection	n	n	
Accidental death / suicide	n	n	
Unknown cause	**n**	**n**	

Note: For a manuscript I would envisage simply using footnotes in each of the diagnosis total to detail how many of the specific WTS events were associated with a death, but for programming efficiency for this analysis it would be easier to have a separate table.

Table 3.3: Incidence of Clinical Events

	Treatment Group						
	Delayed			Immediate			
	#events[1]	/PY	Incidence [95% CI][2]	#events	/PY	Incidence [95% CI]	P-value
Primary clinical events	179	/3567	x/100PY [xx, xx]				
Deaths							
AIDS defining events[3]	51						
Non-AIDS defining events[4]	54						
Tuberculosis							
Malignancies[5]	51						
Cardiovascular/vascular disease events[6]	8						
All targeted clinical events[7]							
All targeted clinical events, sensitivity[8]							

[1] *May include multiple events experienced by one individual*

[2] *Estimated using poission regression with GEE to adjust for repeated events*

[3] *WHO stage 4 events, TB and serious bacterial infections*

[4] *All primary clinical events excluding WHO stage 4 events, TB and serious bacterial infections*

[5] *All malignancies (excluding squamous and basal skin cancer) including the WHO stage 4 events of invasive cervical carcinoma, Kaposi's sarcoma, and confirmed lymphomas.*

[6] *MI, CAD (not including MI), congestive heart failure, or stroke.*

[7] *Includes all clinical events highlighted in Tables 1.1 and 1.2.*

[8] *Includes all clinical events highlighted in Tables 1.1 and 1.2 with the exception of those without firm diagnostic criteria (as highlighted in Table 1.2).*

Table 3.4: Summary of Primary Events

	Treatment Group		
	Delayed N (%)[1]	**Immediate N (%)[1]**	**Total**
Subjects experiencing at least one primary event	**179 (10%)**	**40 (2%)**	**219 (12%)**
Subjects experiencing at least one AIDS defining event	**51 (3%)**	**1 (0%)**	**52 (3%)**
WHO Stage 4 (excl. TB)	54 (3%)	1 (0%)	55 (3%)
Esophageal candidiasis	N	N	
Cervical carcinoma	n	n	
<List of each event>			
Tuberculosis	54 (3%)	1 (0%)	55 (3%)
Serious bacterial infections	51 (3%)	1 (0%)	52 (3%)
Subjects experiencing at least one non-AIDS event	**51 (3%)**	**1 (0%)**	**52 (3%)**
Serious liver disease	51 (3%)	1 (0%)	52 (3%)
End stage renal disease	51 (3%)	1 (0%)	52 (3%)
Non AIDS malignancy[2]	51 (3%)	1 (0%)	52 (3%)
Breast cancer			
<list of each type of cancer observed>			
Diabetes mellitus	51 (3%)	1 (0%)	52 (3%)
Cardiovascular/Vascular disease	8 (2%)	4 (0%)	45 (2%)
Myocardial Infarction	5	N	N
Coronary artery disease (not MI)	2	N	N
Stroke			
Congestive heart failure	3	N	N
Deaths from other causes[3]			

[1] *Gives N (%) of subjects experiencing at least once event of a given category or specific diagnosis; multiple diagnoses of the same specific diagnosis are counted only once; multiple events in the same diagnosis category are counted only once in event category totals.*

[2] *Excluding squamous and basal skin cancer.*

[3] *Deaths associated with a specific primary event are counted in the primary event totals.*

Table 3.5: Median (Q1-Q3) HIV-1 RNA and CD4 cell count Summary of Primary Events

	HIV-1 RNA level		**CD4 cell count**	
	Delayed	**Immediate**	**Delayed**	**Immediate**
At primary clinical event	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**
At death				
At AIDS defining event	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**
Any WHO Stage 4 (excl. TB)	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**
Oesophageal candidiasis	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)
Cervical carcinoma	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)
….	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)
At any Tuberculosis				
At serious bacterial infection				
At non-AIDS event	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**	**Median (Q1-Q3)**
At serious cardiovascular/vascular disease				
At malignancy[1]				

[1] *All malignancies (excluding squamous and basal skin cancer) including the WHO stage 4 events of invasive cervical carcinoma, Kaposi's sarcoma, and confirmed lymphomas.*

Figure 3.1: Distribution of CD4 cell count at the time of targeted event

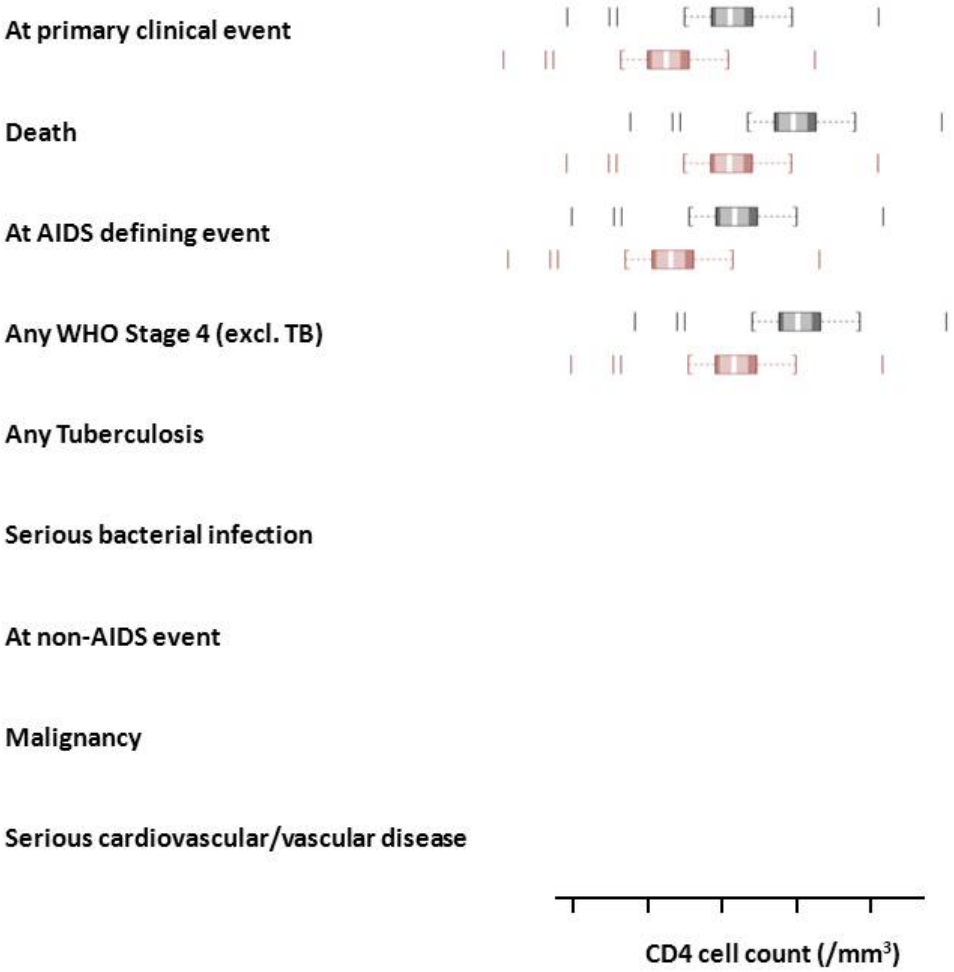

Table 3.6: Descriptive summary of TB cases

	PID	DIAGNOSIS	CRITERIA	STUDY SITE	STUDY ARM	AGE / GEND-ER	DURATION ART WEEKS / STUDY WEEK	CD4 CELL COUNT / HIV RNA	EXTRA-PULMONARY / PULMONARY	CHEST RADIO-GRAPH	SPUTUM SMEAR	SPUTUM CULTURE	TB TREAT-MENT STARTED –Y/N
1	568-054	Abdominal TB;	CLINICAL Abdominal ultrasound with multiple focal splenic lesions	Pune	Delayed					Negative	ND	ND	Y
2	632-183	TB Lymphadonitis (cervical)	Cervical lymph node histology	Lilong-we	delayed					ND	ND	ND	
3	5079 - 077	TB Lymphadonitis (cervical)	AFB smear positive on lymph node	Thabanol	?					Negative	ND	ND	Y
4	543-111	TB Lymphadonitis	Lymph node histology coexisting something?	Harare	?					ND	ND	ND	Y
5	593-073	TB Lymphadonitis	AFB smear positive on lymph node	Port Allegre, Brazil	?					ND	ND	ND	Y

Table 3.7: Summary of Other HIV-1 Associated and Targeted Medical Conditions

	Treatment Group		
	Delayed N (%)[1]	**Immediate N (%)[1]**	**Total**
Subjects experiencing at least one targeted event[2]	**XX (XX%)**	**XX (XX%)**	**XX (XX%)**
Subjects experiencing at least one targeted event, sensitivity[3]	**179 (10%)**	**40 (2%)**	**219 (12%)**
Subjects experiencing at least one secondary event[4]	**51 (3%)**	**1 (0%)**	**52 (3%)**
Subjects experiencing at least one secondary sensitivity[5]			
WHO Stage 2 or 3	54 (3%)	1 (0%)	55 (3%)
Moderate unexplained weight loss[6]			
Upper respiratory tract infection			
Herpes Zoster			
….			
Smear positive malaria	n	n	
Chronic renal insufficiency			
Hepatic transaminitis	54 (3%)	1 (0%)	55 (3%)
Lipodystrophy[6]			
Dyslipidemia			
Peripheral neuropathy	51 (3%)	1 (0%)	52 (3%)
Hypertension[6]	**51 (3%)**	**1 (0%)**	**52 (3%)**
Lactic acidosis (symptomatic)	51 (3%)	1 (0%)	52 (3%)
Thrombocytopenia	51 (3%)	1 (0%)	52 (3%)

[1] Gives N (%) of subjects experiencing at least once event of a given category or specific diagnosis; multiple diagnoses of the same specific diagnosis are counted only once; multiple events in the same diagnosis category are counted only once in event category totals.

[2] Any of the targeted events given in Table 1.1 and 1.2.

[3] Any of the targeted clinical events highlighted in Tables 1.1 and 1.2 with the exception of those without firm diagnostic criteria (as highlighted in Table 1.2).

[4] Any of the targeted events given in Table 1.2.

[5] Any of the targeted clinical events highlighted in Table 1.2 with the exception of those without firm diagnostic criteria (as highlighted in Table 1.2).

[6] Excluded in sensitivity analysis.

	Qualifying outcomes (unless noted otherwise, diagnostic criteria were based on the ACTG Appendix 60 criteria and underwent blinded review)
AIDS-defining outcomes	
WHO stage 4	Recurrent severe bacterial pneumonia (>2 episodes in 12 months); Oesophageal candidiasis (or candidiasis of bronchi, trachea, or lungs); Invasive cervical carcinoma (confirmed by biopsy); Chagas' disease; Extrapulmonary cryptococcosis (including meningitis); Chronic intestinal cryptosporidiosis (>1 month duration); Cytomegalovirus disease (retinitis or infection of other organs); HIV-related encephalopathy; Chronic herpes simplex (orolabial, genital, or anorectal site, >1 month duration), or bronchitis, pneumonitis, oesophagitis, or visceral at any site; Chronic intestinal isosporiasis (>1 month duration, confirmatory diagnostic testing required); Kaposi's sarcoma; Atypical, disseminated Leishmaniasis; Lymphoma (Burkitt, immunoblastic, primary CNS/cerebral, B-cell non Hodgkin, confirmatory diagnostic testing required); *Mycobacterium avium* complex; Disseminated or extrapulmonary *Mycobacterial kansasii*; Disseminated or extrapulmonary mycobacterial infection (other or unidentified species); Disseminated mycosis, extrapulmonary histoplasmosis; coccidiomycosis; Disseminated penicilliosis; Pneumocystis pneumonia; Progressive multifocal leukoencephalopathy; Recurrent septicemia (including non-typhoidal Salmonella); Symptomatic HIV-associated nephropathy or symptomatic HIV associated cardiomyopathy; Toxoplasmosis of brain/CNS; Wasting syndrome due to HIV (involuntary weight loss >10% of baseline bodyweight) associated with either chronic diarrhoea (>2 loose stools per day >1 month) or chronic weakness and documented fever >1 month
Tuberculosis	Extrapulmonary and pulmonary *Mycobacterium tuberculosis*
Severe bacterial infections	For example, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia
Non-AIDS defining outcomes	
Serious liver disease	Limited to presence of cirrhosis, esophageal varices, hepatic encephalopathy, hepatic failure or hepatic encephalopathy. *Repeat events were not included; such events were queried for reconciliation.*

Serious cardiovascular or vascular disease	Limited to myocardial infarction, coronary artery disease (not myocardial infarction), congestive heart failure and stroke events
End-stage renal disease	Two consecutive measurements of grade 4 serum creatinine (>3.5 x upper limit of normal) or need for dialysis. *Repeat events were not included; such events were queried for reconciliation.*
Non-AIDS malignant disease	Excluding squamous and basal skin cancer
Diabetes mellitus	Incident diagnoses of participants with evidence of pre-existing diabetes mellitus were excluded. *Repeat events were not included; such events were queried for reconciliation.*
Death	Unrelated to other primary clinical event (including deaths related to primary event diagnoses that did not meet Appendix 60 endpoint criteria).

Table 1: **Definition of primary outcomes**

	Qualifying outcomes (unless noted otherwise, diagnostic criteria were based on the ACTG Appendix 60 criteria and underwent blinded review)
WHO stage 2	Moderate, unexplained weight loss (<10% bodyweight); Recurrent upper-respiratory-tract infections (sinusitis, tonsillitis, otitis media, and pharnygitis); Herpes zoster; Angular cheilitis; Recurrent oral ulcerations; Papular puritic eruptions; Seborrhoeic dermatitis; Fungal nail infections.
WHO stage 3	Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis; Unexplained severe weight loss (>10% bodyweight); Unexplained chronic diarrhoea; Unexplained persistent fever; Persistent oral candidiasis; Oral hairy leukoplakia; Unexplained anaemia
Malaria	Confirmed by peripheral blood smear or rapid diagnostic testing
Chronic renal insufficiency	Defined as serum creatinine 1.0–3.5 x upper limit of normal (grade 3) for a period of 3 months or more
Hepatic transaminitis	2 or more consecutive grade 3 or higher liver function tests (ALT/AST/ALP/total bilirubin) within a 1 year period excluding isolated (ie, in the absence of other elevated liver enzymes) ATV-associated hyperbilirubinaemia
Lipodystrophy	Clinical diagnosis including facial and peripheral fat loss, central obesity and/or dorsocervical fat pad
Dyslipidaemia	Any grade 3 or higher LDL or total cholesterol; cases were determined based on a single value *Repeat events were not included.*
Peripheral neuropathy	Incident diagnoses; diagnoses in participants with evidence of pre-existing peripheral neuropathy (diagnosis date on or before randomization) were excluded
Hypertension	Incident diagnoses of participants with evidence of pre-existing and ongoing hypertension (onset date on or before randomization) were excluded
Lactic acidosis (symptomatic)	Lactate level ≥2 x upper limit of normal with accompanying symptoms
Thrombocytopenia	Cases were defined as participants with 2 or more grade 3 or higher platelet counts (<50 000 cells per μL) within a 1-year period

Table 2: **Definition of secondary outcomes**

	Study Site	Study Arm	Age/Sex	Study week	ART week	CD4+	HIV RNA	Radiographic findings	Sputum smear	Sputum culture	Other results	TB treatment started
1	Gaborone	Immediate	27/Female	25	25	658	<400	Right cavitation & reticulonodular infiltrate	Positive	ND		Y
2	Harare	Delayed	52/Male	116	59	219	<400	Shadowing mid and lower zones-miliary pattern	Positive	ND		Y
3	Harare	Delayed	54/Male	52		279	750000	Unilateral infiltrate with cavitary lesion	Positive	ND		Y
4	Harare	Delayed	54/Male	128		449	750000	Unilateral infiltrate with adenopathy	Negative	ND		Y
5	Harare	Delayed	48/Male	74		377	56632	Pleural effusion	Negative	ND		Y
6	Harare	Delayed	26/Female	4		577	13815	ND	ND	ND	Caseating granuloma in lymph node	Y
7	Harare	Delayed	26/Female	59		499	41753	ND	ND	ND	Caseating granuloma in lymph node	Y
8	Harare	Delayed	26/Female	19		272	390805	Extensive consolidation in both lungs	ND	ND		No*
9	Chennai	Immediate	41/Male	59	59	571	<400	Unilateral infiltrate	Positive	ND		Y
10	Chennai	Immediate	35/Male	1	1	373	66600	ND	ND	ND		Y
11	Chennai	Delayed	45/Male	8		389	750000	Mediastinal adenopathy	ND	ND		Y
12	Chennai	Immediate	28/Male	142	142	196	37600	ND	ND	ND	AFB + in lymph node	Y
13	Chennai	Immediate	40/Male	64	64	426	<400	Unilateral infiltrate	ND	ND		Y

14	Chennai	Delayed	35/Male	84	2	128	81700	Normal	Positive	ND		Y
15	Chennai	Immediate	43/Male	151	151	461	<400	Unilateral infiltrate	ND	ND		Y
16	Chennai	Delayed	21/Female	66		396	750000	Bilateral infiltrate	ND	ND		Y
17	Chennai	Delayed	21/Female	155	48	285	750000	Unilateral infiltrate	ND	ND		Y
18	Chennai	Delayed	32/Male	152		306	536000	Normal	ND	ND	Mesenteric adenopathy on abdominal ultrasound	Y
19	Chennai	Delayed	40/Male	34		267	724000	Bilateral infiltrate	ND	ND		Y
20	Chennai	Delayed	30/Male	64		265	750000	Hilar infiltrate	ND	ND		Y
21	Chennai	Delayed	35/Male	77		585	750000	Unilateral infiltrate	Negative	ND		Y
22	Chennai	Immediate	44/Male	9	9	377	<400	Unilateral infiltrate	ND	ND		Y
23	Chennai	Immediate	38/Male	129	129	574	<400	Chest CT with multiple adenopathies	ND	ND		Y
24	Chennai	Immediate	46/Male	105	105	351	<400	Bilateral infiltrate	Negative	Negative		Y
25	Chennai	Delayed	35/Male	97		271	134000	Normal	ND	ND	Retroperitoneal adenopathy on abdominal ultrasound	Y
26	Chennai	Delayed	27/Male	104		319	62200	Unilateral infiltrate	ND	ND		Y
27	Chennai	Delayed	39/Male	114		425	281000	Normal	Positive	ND	Adenopathy on abdominal ultrasound	Y
28	Chennai	Immediate	49/Male	117	117	496	1330	Unilateral infiltrate	ND	ND		Y
29	Chennai	Delayed	26/Female	77		434	414000	Bilateral infiltrate	ND	ND		Y
30	Chennai	Immediate	40/Male	76	76	518	<400	Cavitary lesion	ND	ND		Y

31	Chennai	Immediate	35/Male	26	26	716	<400	Marginal erosion of carpal bones on wrist CT scan	ND	ND		Y
32	Chennai	Delayed	31/Male	84	3	228	379000	Bilateral infiltrates	ND	ND		Y
33	Pune	Delayed	33/Male	13		324	50100	Vertebral collapse and abscess on lumbar spine XR and MRI	ND	ND		Y
34	Pune	Delayed	35/Female	27		342	119000	ND	ND	ND	Ascitic fluid 95% lymphocytes	Y
35	Pune	Delayed	53/Male	247	0	86	8410	Abdominal ultrasound & CT scan consistent with TB	ND	ND		Y
36	Pune	Delayed	34/Male	140		301	148000	Normal chest x ray; abdominal ultrasound & CT scan with mesenteric adenopathy	ND	ND		Y
37	Pune	Delayed	40/Male	77		379	212000	Normal chest x-ray; abdominal ultrasound with mesenteric adenopathy	ND	ND	Cervical lymph node histology with caseating granuloma	Y
38	Pune	Immediate	27/Male	42	42	443	<400	Pleural effusion	Positive	ND	Pleural fluid with lymphocytosis	Y
39	Pune	Delayed	41/Male	8		637	39400	Normal chest x-ray; abdominal ultrasound with multiple splenic lesions	ND	ND		Y

40	Chiang Mai	Immediate	26/Female	202	202	668	<400	Normal	ND	ND	AFB + on lymph node	Y
41	Porto Alegre	Delayed	37/Female	66		509	264000	ND	ND	ND	AFB + on lymph node	Y
42	Rio de Janeiro	Delayed	43/Male	49		304	750000	Chest CT scan with left pulmonary infiltrate	Negative	Positive		Y
43	Rio de Janeiro	Delayed	37/Female	100		311	4435	Bilateral infiltrate with bibasal condensation	Negative	ND		Y
44	Johannesburg	Delayed	43/Male	77		179	666000	Right lower lobe consolidation & patchy infiltrates	NA	Positive		Y
45	Johannesburg	Delayed	52/Female	45		277	403000	Bibasal patchy infiltrates & proeminent hilum	NA	Negative		Y
46	Johannesburg	Immediate	36/Female	12	10	525	<400	ND	Negative	Positive		Y
47	Lilongwe	Immediate	38/Male	124	124	524	750000	Left lower lobe infiltrate	ND	ND		Y
48	Blantyre	Delayed	33/Female	29		316	1265	Left pleural effusion	Negative	ND	Pleural fluid lymphocytosis	Y
49	Lilongwe	Delayed	28/Female	51		256	507812	ND	ND	ND	AFB + on lymph node	Y
50	Lilongwe	Delayed	33/Female	51		474	30303	ND	ND	ND	Cervical lymph node histology	Y
51	Lilongwe	Delayed	44/Female	3		316	9726	ND	ND	ND	Pleural fluid with lymphocytosis	Y
52	Blantyre	Delayed	38/Male	52		330	88478	Cavitary lesions	Negative	ND		Y
53	Blantyre	Delayed	50/Male	24		302	683166	ND	ND	ND	CSF lymphocytosis & low glucose	Y

54	Soweto	Immediate	30/Female	35	35	411	<400	Right upper lobe infiltrate	Negative	Positive		Y

* Patient died before starting TB treatment

Table 3: **Tuberculosis cases**

Note: Number events sequentially (01, 02, 03). Number each page with the same event number. **Event Number** ☐☐

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Index ID

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Index When to Start

diagnosis code

1. Record diagnosis code for this event: ☐☐

1a. Specify diagnosis: _____

confirmed *probable*

1b. Indicate if diagnosis is confirmed or probable:..... ☐ ☐

yes *no*

1c. Is this an AIDS-defining illness? ☐ ☐

1d. Indicate the Visit Code at which this event was first reported: ☐☐.☐

1e. Was this event recorded on the Index Adverse Events Log? *yes* ☐ *no* ☐ → *Record AE Log Page #* ☐☐☐

1f. Diagnosis status: *new* ☐ *recurrent* ☐

dd *MMM* *yy*

1g. Date event started: ☐☐ ☐☐☐ ☐☐

1h. Date of diagnosis: ☐☐ ☐☐☐ ☐☐

1i. Outcome:

☐ Continuing

☐ Resolved

☐ Death

1i1. Date of outcome: *dd* ☐☐ *MMM* ☐☐☐ *yy* ☐☐

☐ Continuing at end of study participation

2. Is diagnosis a clinical event with a code of 30–44?..... *yes* ☐ *no* ☐

→ ***If yes, end of form. Fax only page 1 to SCHARP DataFax.***

Comments: _____

_____

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Index When to Start (IWT-1)

The Index When to Start CRF collects data on HIV/AIDS-related illnesses, WHO Stage 2 and 3 Clinical Events, and other targeted conditions, according to LOA #1 to version 3.0 of the protocol. Fax the form within 3 weeks of first becoming aware of the event.

Events listed in Appendix IV as HIV/AIDS-related illnesses (codes 01–28) and Other Targeted Medical Conditions (codes 50–63) require completion of all pages of the CRF. All other events (codes 30–44) require completion of page 1 only; any pertinent information related to the diagnosis (e.g., diagnosis confirmed via test) may be recorded on the Comments line.

Event Number: Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Index When to Start pages after faxing, unless instructed by SCHARP.

Item 1 Diagnosis Code: Refer to the Code Lists below. If a diagnosis is later found to be incorrect, draw a line through the diagnosis code and record the correct code.

HIV/AIDS-related Illnesses (WHO Stage 4, severe bacterial infections and pulmonary TB) **Code List**

- 01 Bacterial infections, severe (WHO Stage 3) (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- 02 Bacterial pneumonia, recurrent, severe (≥ 2 episodes in 12 months)
- 03 Oesophageal candidiasis (or candidiasis of bronchi, trachea, or lungs)
- 04 Cervical carcinoma, invasive, confirmed by biopsy
- 05 Chagas' disease
- 06 Cryptococcosis, extrapulmonary including meningitis
- 07 Cryptosporidiosis, chronic intestinal (> 1 month duration)
- 08 Cytomegalovirus disease (retinitis or infection of other organs)
- 09 Encephalopathy, HIV-related
- 10 Herpes simplex, chronic (orolabial, genital, or anorectal site, > 1 month duration), or bronchitis, pneumonitis, esophagitis, or visceral at any site
- 11 Isosporiasis, chronic intestinal (> 1 month duration) (confirmatory diagnostic testing required)
- 12 Kaposi's sarcoma
- 13 Leishmaniasis, atypical, disseminated
- 14 Lymphoma, Burkitt, immunoblastic, primary central nervous system/ cerebral, B cell non Hodgkin (confirmatory diagnostic testing required)
- 15 *Mycobacterium avium* complex (MAC)
- 16 *M. kansasii*, disseminated or extrapulmonary
- 17 *Mycobacterium tuberculosis*, pulmonary (WHO Stage 3)
- 18 *Mycobacterium tuberculosis*, extrapulmonary
- 19 Mycobacterial infection, other species or unidentified species, disseminated or extrapulmonary
- 20 Mycosis, disseminated, extrapulmonary histoplasmosis
- 21 Mycosis, disseminated, coccidiomycosis
- 22 Penicilliosis, disseminated
- 23 Pneumocystis pneumonia
- 24 Progressive multifocal leukoencephalopathy (PML)
- 25 Septicemia, recurrent, including non-typhoidal *Salmonella*
- 26 Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy
- 27 Toxoplasmosis of brain/central nervous system
- 28 Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥ 2 loose stools per day ≥ 1 month) or chronic weakness and documented fever ≥ 1 month (MAC)

WHO Stage 2 and 3 Clinical Events Code List (excluding pulmonary TB and severe bacterial infections; see HIV/AIDS-related Illnesses Code List above)

Stage 2

- 30 Moderate, unexplained weight loss (< 10% body weight)
- 31 Upper respiratory tract infections, recurrent (sinusitis, tonsillitis, otitis media and pharnygitis)
- 32 Herpes zoster
- 33 Angular cheilitis
- 34 Oral ulcerations, recurrent
- 35 Papular puritic eruptions
- 36 Seborrhoeic dermatitis
- 37 Fungal nail infections

Stage 3

- 38 Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- 39 Unexplained severe weight loss (> 10% body weight)
- 40 Unexplained chronic diarrhea
- 41 Unexplained persistent fever
- 42 Oral candidiasis, persistent
- 43 Oral hairy leukoplakia
- 44 Unexplained anemia

Other Targeted Medical Conditions Code List

- 50 Diabetes mellitus
- 51 Lipodystrophy
- 52 Dyslipidemia
- 53 Malaria
- 54 Sensory peripheral neuropathy
- 55 Hypertension
- 56 Myocardial infarction
- 57 Coronary artery disease, not myocardial infarction
- 58 Congestive heart failure, not HIV cardiomyopathy
- 59 Stroke
- 60 Malignancy, newly diagnosed, excluding squamous cell and basal cell cancer of the skin
- 61 Renal insufficiency
- 62 Liver disease
- 63 Lactic acidosis

Item 1d: Record the visit code at which the event or illness was first reported.

Item 1f: Recurrent is defined as an event that recurs after it has clinically resolved after treatment.

Item 1g: Date event started is the date on which issues or symptoms related to the event started. At minimum, month and year are required.

Item 1h: Date of diagnosis is the date on which the confirmed or probable diagnosis was made. If a diagnosis is later found to be incorrect, draw a line through the diagnosis date and record the date of the correct diagnosis.

Item 1i: At the participant's Termination visit, the "Resolved" box must be marked and the date recorded for each event or illness OR the "Continuing at end of study participation" box must be marked.

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Note: Number events sequentially (01, 02, 03). Number each page with the same event number. **Event Number** ☐☐

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Index When to Start

Diagnosis Code ☐☐

3. Complete the information below for each abnormal laboratory result that supports or confirms the diagnosis.

OR ☐ No laboratory results to report. → ***Go to item 4.***

	Test Code	Date Specimen Obtained (dd MMM yy)	Laboratory Value	Units Code
3a.	☐☐☐☐	☐☐ ☐☐☐ ☐☐	☐☐☐☐☐☐☐.☐☐☐	☐☐
3b.	☐☐☐☐	☐☐ ☐☐☐ ☐☐	☐☐☐☐☐☐☐.☐☐☐	☐☐
3c.	☐☐☐☐	☐☐ ☐☐☐ ☐☐	☐☐☐☐☐☐☐.☐☐☐	☐☐
3d.	☐☐☐☐	☐☐ ☐☐☐ ☐☐	☐☐☐☐☐☐☐.☐☐☐	☐☐
3e.	☐☐☐☐	☐☐ ☐☐☐ ☐☐	☐☐☐☐☐☐☐.☐☐☐	☐☐
3f.	☐☐☐☐	☐☐ ☐☐☐ ☐☐	☐☐☐☐☐☐☐.☐☐☐	☐☐

4. Were any other diagnostic tests used to establish/ confirm this diagnosis? ..... *yes* ☐ *no* ☐

→ ***If yes, go to item 4b.***

4a. If no, how was the diagnosis made?

Specify: _____

_____

→ ***Go to item 5.***

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Index When to Start (IWT-2)

Diagnosis Code: Record the code reported in item 1 on page 1.

Items 3a–3f Test Code: Refer to the Master CRF Appendices Notebook or on ACTG's DMC Website (http://fstrf.org/ACTG) for Appendix 76 for a complete list of codes.

ALB	albumin	CRET	creatinine (ULN)	K	potassium
ALP	alkaline phosphatase	FHDL	fasting HDL	MCV	mean corpuscular volume
ALT	(SGPT) (ULN)	FTC	fasting total cholesterol	NA	sodium
LST	(SGOT) (ULN)	FTG	fasting triglycerides	P	phosphate
CFLD	calculated fasting LDL	GLOC	glucose	PLAT	platelets
CL	chloride	HCO3	bicarbonate	RBC	red blood cells
CO2	carbon dioxide	HGB	hemoglobin	TBIL	total bilirubin (ULN)
				WBC	white blood cells

Items 3a–3f Units Code: For laboratory tests listed in the DAIDS Toxicity Tables where Conventional and/or Standard International Units (IU) are identified, the result value must be reported in one of the units of measurement listed in the table. If a different unit of measurement is reported by the laboratory the result value must be converted to either the conventional or standard units listed in the DAIDS Table.

11	cubic microns	24	μKat/L	37	mm/hr	50	x 10^3/cu mm
12	fL	25	μL	38	million/mL	51	x 10^9/L
13	g/d	26	μmol/L	39	mmol/L	52	x 10^{12}/L
14	g/dL	27	mg/dL	40	ng/dL	53	x 10^3/μL
15	g/L	28	mg/g stool	41	ng/mL	54	x 10^6/μL
16	IU/L	29	mg/L	42	nmol/L	55	times viscosity of water
17	IU/mL	30	mg/24 h	43	% (percent)	56	tuberculin
18	kU/L	31	mEq/L	44	% saturation	57	units
19	microns	32	mIU/L	45	% total hemoglobin	58	U/g hemoglobin
20	μg/dL	33	mL/min	46	pg	59	U/L
21	μg/L	34	mU/$_3$mL	47	pg/mL	60	U/mL
22	μg/mL	35	mm^3	48	pmol/L	61	volume fraction
23	μIU/mL	36	mm Hg	49	seconds	98	no units identified on report

Note: Number events sequentially (01, 02, 03). Number each page with the same event number. **Event Number** ☐☐

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Index When to Start

Diagnosis Code ☐☐

Complete the information below for each test. For diagnoses of tuberculosis, list all diagnostic tests regardless of result.

	Test Type	Result Code	Date Specimen Obtained/Test Done (dd-MMM-yy)	Specify Test, Site, Units	Specify Result
4b.	☐	☐	☐☐ ☐☐☐ ☐☐		
4c.	☐	☐	☐☐ ☐☐☐ ☐☐		
4d.	☐	☐	☐☐ ☐☐☐ ☐☐		
4e.	☐	☐	☐☐ ☐☐☐ ☐☐		
4f.	☐	☐	☐☐ ☐☐☐ ☐☐		
4g.	☐	☐	☐☐ ☐☐☐ ☐☐		

5. Was the index receiving any antiretroviral or other medications at the time of this diagnosis which are known or suspected to be related to the event?..... *yes* ☐ *no* ☐ → ***If no, go to item 6.***

Complete the information below for each medication.

	Drug Code	Relationship of diagnosis to Medication/Treatment *Mark only one.*	Action Taken with Medication *Mark only one.*
5a.	☐☐☐☐☐☐☐☐ specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued
5b.	☐☐☐☐☐☐☐☐ specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued

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Index When to Start (IWT-3)

Diagnosis Code: Record the code reported in item 1 on page 1.

Items 4b–4g Test Type:

1	Culture
2	Antigen Assay
3	Antibody
4	Microscopy/pathology/biopsy
5	Radiology
6	Other laboratory
9	Other

Items 4b–4g Result Code:

1	Normal
2	Abnormal, consistent with reported event
3	Abnormal, not consistent with reported event
4	Inconclusive
5	Inadequate/insufficient
6	Result pending
9	Other

Items 5a–5b Drug Code: Refer to Appendix 3 or the Drug Code Lookup Program on ACTG's DMC Website (http://fstrf.org/ACTG) for drugs not listed below.

08180407	Abacavir Sulfate/ABC/Ziagen	08180415	FTC/Emtriva/emtricitabine
08180208	Aluvia (lopinavir/ritonavir)	08180043	Indinavir/IDV/Crixivan
08181205	Amprenavir/APV/Agenerase	08181218	Lexiva/Fosampreavir
08181214	Atazanavir/ATV/Reyataz	08180026	Lamivudine/3TC/Epivir
08180422	Atripla (efavirenz/emtricitabine/TDF)	08181208	Lopinavir/Ritonavir (LPV/RTV)/Kaletra
08180021	AZT/ZDV/Zidovudine/Retrovir	08181204	Nelfinavir/NFV/Viracept
08180412	Combivir (3TC/ZDV)	08180013	Nevirapine/NVP/Viramune
08180024	d4T/Stavudine/Zerit	08181203	Ritonavir/RTV/Norvir
08180414	DAPD/Amdoxovir/trimeric	08181209	Saquinavir soft gel/FTV/Fortovase
08180020	ddC/Zalcitabine/Hivid	08180030	Saquinavir/SQV/Invirase/R031-8959
08180007	ddI/Didanosine/Videx	08188804	T-20/pentafuside/enfuvirtide/ENF/Fuzeon
08180051	ddI ECDidanosine EC/Videx EC	08182002	TDF/Tenofovir/Tenofovir disoproxil fumarate/Viread
08180031	DLV/delavirdine mesylate/Rescriptor	08180418	Trizivir (3TC/ABC/ZDV)
08180804	Efavirenz/EFV/Sustiva/StocrinR	08180421	Truvada (tenofovir disoproxil/emtricitabine)
08180420	Epzicom (Abacavir/lamivudine)		

Note: Number events sequentially (01, 02, 03). Number each page with the same event number. **Event Number** ☐☐

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Index When to Start

Diagnosis Code ☐☐

	Drug Code	Relationship of diagnosis to Medication/Treatment *Mark only one.*	Action Taken with Medication *Mark only one.*
5c.	☐☐☐☐☐☐☐☐ specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued
5d.	☐☐☐☐☐☐☐☐ specify: _____	☐ definitely related ☐ possibly related ☐ probably related ☐ probably not related	☐ dose reduced ☐ no change ☐ withheld ☐ permanently discontinued

6. Were specific treatments recommended or initiated to treat this diagnosis? ..... *yes* ☐ *no* ☐ → ***If no, go to item 7.***

6a. If yes, did this lead to an improvement in the condition? ..... *yes* ☐ *no* ☐

Complete the information below for each therapy.

	Drug Code	Specify
6a1.	☐☐☐☐☐☐☐☐	
6a2.	☐☐☐☐☐☐☐☐	
6a3.	☐☐☐☐☐☐☐☐	
6a4.	☐☐☐☐☐☐☐☐	
6a5.	☐☐☐☐☐☐☐☐	
6a6.	List any other treatments recommended, e.g. diet, exercise:	

7. Was any other information used to arrive at this diagnosis? *yes* ☐ *no* ☐ → ***If no, end of form.***

7a. If yes, specify: _____

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Index When to Start (IWT-4)

Diagnosis Code: Record the code reported in item 1 on page 1.

Items 5c–5d Drug Code: Refer to Appendix 3 or the Drug Code Lookup Program on ACTG's DMC Website (http://fstrf.org/ACTG) for drugs not listed below.

Items 6a1–6a5 Drug Code: Refer to Appendix 3 or the Drug Code Lookup Program on ACTG's DMC Website (http://fstrf.org/ACTG).

08180001	Acyclovir	08160008	Isoniazid
48160023	Ambroxol hydrochloride	08400014	Itraconazole
08121610	Amoxicillin trihydrate	08220009	Levofloxacin
08120401	Amphotericin B	56400004	Metoclopramide
08400001	Azithromycin	84041623	Metronidazole (topical)
08120614	Cephalexin	08040001	Metronidazole
08220002	Ciprofloxacin	08120406	Miconazole
08121203	Clarithromycin	88280009	Multiple Vitamins
08122803	Clindamycin HCL	48240001	N-acetylcysteine; acetylcysteine
28120801	Clonazepam	08120407	Nystatin (oral)
08260001	Dapsone	84040816	Nystatin (topical)
68320002	Depo-Provera (medroxyprogesterone acetate)	28089201	Paracetamol
84060010	Dexamethasone (topical)	08121601	Penicillin G benzathine
04120023	Dexchlorpheniramine maleate	08400009	Pentamidine isethionate
28080443	Diclofenac potassium	80120011	Pneumococcal vaccine, polyvalent
28080417	Diclofenac sodium	08160010	Pyrazinamide
28080457	Dipyrone	08200006	Pyrimethamine
08122403	Doxycycline hyclate	08160011	Rifampin
08160006	Ethambutol	12080826	Scopolamine
08160007	Ethionamide	08120206	Streptomycin sulfate
20040405	Ferrous sulfate	08240005	Sulfadiazine
08120402	Fluconazole	08400005	Sulfamethoxazole; comb.; trimethoprim; (co-trimoxazole)
88080006	Folinic acid		
08180046	Ganciclovir	80080002	Tetanus and diphtheria toxoids adsorbed (for adult use)
80120022	Hepatitis A vaccine	84360015	Trichloroacetic acid
80120057	Hepatitis A virus vaccine inactivated and Hepatitis B vaccine (recombinant)	08180022	Valacyclovir HCL
		08812001	Vitamin C
80120006	Influenza virus vaccine		

APPENDIX 60

Version 1.3

April, 2011

TABLE OF CONTENTS

I. PARASITIC INFECTIONS

CHAGAS' DISEASE - CENTRAL NERVOUS SYSTEM INVOLVEMENT

61030 CONFIRMED

At least one of the following:

a. Direct finding of Trypanosomes in liquor, or brain biopsy

and

b. CSF pleocytosis, increased protein and occasionally decreased glucose levels

61031 PROBABLE

1. Person came from endemic area

and

2. CNS mass lesion with contrast enhancing effect that does not improve with Toxoplasmic treatment

and

3. CSF pleocytosis, increased protein and occasionally decreased glucose levels

and

4. Positive serology

CHAGAS' DISEASE - MYOCARDITIS

61032 CONFIRMED

1. Finding of Trypanosomes nests in myocardium biopsy or in buffy coat

and

2. EKG right bundle branch block

61033 PROBABLE

1. Person came from endemic area

and

2. Clinical myocarditis

and

3. EKG with a variety of disturbances, most commonly right bundle branch block

and

4. Positive serology

CRYPTOSPORIDIOSIS

61035 CONFIRMED

1. At least one of the following:
    a. Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
    b. Presence of at least one of the following abdominal symptoms: nausea, vomiting or abdominal pain.
    c. Presence of at least one of the following: biliary colic, jaundice or elevation in total bilirubin, alkaline phosphatase or gamma-glutamyl transpeptidase (GGTP) greater than or equal to 2.5 times the upper limit of normal (ULN.)

and

2. Microscopic evidence of cryptosporidium present in stool, body fluid or tissue specimen.

PROBABLE

There is no acceptable definition to be used within the ACTG.

CYCLOSPORA GASTROENTERITIS

61015 CONFIRMED

1. At least one of the following:
    a. Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
    b. Presence of at least one of the following abdominal symptoms: nausea, vomiting or abdominal pain.
    c. Presence of at least one of the following: biliary colic, jaundice or elevation in total bilirubin, alkaline phosphatase or gamma-glutamyl transpeptidase (GGTP) greater than or equal to 2.5 times the upper limit of normal (ULN.)

and

2. Microscopic evidence of cyclospora present in stool, body fluid or tissue specimen.

PROBABLE

There is no acceptable definition to be used within the ACTG.

ISOSPORIASIS

61045 CONFIRMED

1. At least one of the following:
    a. Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
    b. Presence of at least one of the following abdominal symptoms: nausea, vomiting or abdominal pain.
    c. Presence of at least one of the following: biliary colic, jaundice or elevation in total bilirubin, alkaline phosphatase or gamma-glutamyl transpeptidase (GGTP) greater than or equal to 2.5 times the upper limit of normal (ULN.)

and

2. Microscopic evidence of isospora present in stool, body fluid or tissue specimen.

PROBABLE

There is no acceptable definition to be used within the ACTG.

LEISHMANIASIS

There are four forms of leishmaniasis: visceral, cutaneous disease, mucosal disease and diffuse cutaneous leishmaniasis. Specify which form of disease.

61048 CONFIRMED

1. Histologic evidence of disease from an aspirate or biopsy.

and

2. Compatible clinical syndrome.

61049 PROBABLE

1. Compatible clinical syndrome.

and

2. Specific treatment initiated or recommended.

MALARIA

61006 CONFIRMED

1. Identification of Plasmodium sp. on a smear of peripheral blood

and

2. Compatible clinical syndrome.

61007 PROBABLE

1. Compatible clinical syndrome

and

2. Specific treatment initiated or recommended.

MICROSPORIDIOSIS

61055 CONFIRMED

1. At least one of the following:
    a. Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
    b. Presence of at least one of the following abdominal symptoms: nausea, vomiting or abdominal pain.
    c. Presence of at least one of the following: biliary colic, jaundice or elevation in total bilirubin, alkaline phosphatase or gamma-glutamyl transpeptidase (GGTP) greater than or equal to 2.5 times the upper limit of normal (ULN.)

and

2. Microscopic evidence of microsporidia present in stool, body fluid or tissue specimen.

PROBABLE

There is no acceptable definition to be used within the ACTG.

PNEUMOCYSTIS CARINII PNEUMONIA (PCP) (also known as Pneumocystis jiroveci pneumonia)

61011 CONFIRMED

1. A history (within the past three months) of shortness of breath, dyspnea on exertion, cough or fever

and

2. Histological or cytological evidence of Pneumocystis carinii on bronchoalveolar lavage, lung biopsy or sputum specimen.

61012 PROBABLE

1. A history (within the past three months) of shortness of breath, dyspnea on exertion, cough or fever

and

2. Abnormal chest X-ray (or CT scan) or hypoxemic arterial blood gas P_aO_2 <80 mmHg or (A-a) DO_2 mm Hg >15, on room air

and

3. Specific anti-pneumocystis therapy was recommended or initiated.

61013

Clinical diagnosis only, clinical history, consistent chest X-ray and improvement on PCP therapy.

EXTRA PULMONARY PNEUMOCYSTOSIS

61017 CONFIRMED

Histological or cytological evidence of extra pulmonary pneumocystosis.

61018 PROBABLE (EYE DISEASE ONLY)

1. Pneumocystis lesions of the retina as indicated by characteristic lesions consistent with Pneumocystis choroiditis according to an experienced ophthalmologist

and

2. Clinical improvement with systemic anti-pneumocystosis therapy.

TOXOPLASMIC ENCEPHALITIS

61020 CONFIRMED

1. Histologic evidence of Toxoplasma gondii in tissue obtained by brain biopsy or autopsy

or

2. All of the following:
    a. Compatible clinical syndrome consisting of headache, seizure, neurologic deficits and/or fever.
    b. Presence of characteristic mass lesion(s) on brain imaging study (CT or MRI).
    c. Response after a minimum of two weeks of antitoxoplasmosis therapy with documented clinical or radiographic improvement.
    d. Positive blood culture for Toxoplasma gondii.

61021 PROBABLE

1. Compatible clinical syndrome consisting of headache, seizure, neurologic deficits and/or fever

and

2. Presence of characteristic mass lesion(s) on brain imaging study (CT or MRI)

and

3. Response after a minimum of two weeks of antitoxoplasmosis therapy with documented clinical or radiographic improvement.

61024

Clinical Diagnosis only, compatible clinical syndrome consisting of headache, seizure, neurologic deficits and/or fever and response after a minimum of two weeks of antitoxoplasmosis therapy with documented clinical improvement.

NON-CNS TOXOPLASMOSIS

61028 CONFIRMED

Histologic evidence of Toxoplasma gondii present in tissue or body fluid obtained by biopsy or aspirate.

PROBABLE

There is no acceptable definition to be used within the ACTG.

II. FUNGAL INFECTIONS

ANGULAR CHEILITIS

65022

Clinical descriptors: Red or white fissures or linear ulcers located at the lip commissures or corners of the mouth.
Patient reported symptoms: None or possible mild pain when opening the mouth.
Patient reported duration: Lesions/symptoms are usually intermittent, but may be long-standing.

DISSEMINATED BLASTOMYCOSIS

62051 CONFIRMED

Evidence of B. dermatitidis by positive culture or positive histopathology identifying characteristic appearance of organisms within body tissue or fluids.

PROBABLE

There is no acceptable definition to be used within the ACTG.

CANDIDIASIS OF BRONCHI, TRACHEA OR LUNGS, SPECIFY SITE (BRONCHI, TRACHEA OR LUNGS)

62080 CONFIRMED

1. Characteristic white plaques in the bronchi or trachea on bronchoscopic examination.

and

2. Positive culture, KOH or histopathology from the bronchi or trachea.

62081 PROBABLE

1. Characteristic white plaques in the bronchi or trachea on bronchoscopic examination.

and

2. Response to specific antifungal therapy.

ESOPHAGEAL CANDIDIASIS

62010 CONFIRMED

1. Compatible clinical syndrome, consisting of one or more of the following signs or symptoms: white plaques in esophagus, typical filling defects on barium swallow, odynophagia (midline retrosternal discomfort with swallowing).

and

2. Positive culture, KOH or histopathology from esophagus.

62011 PROBABLE

1. Either:
    a. Compatible clinical syndrome, consisting of two or more of the following signs or symptoms: white plaques in esophagus; typical filling defects on barium swallow; odynophagia (midline retrosternal discomfort with swallowing)

    or:

    b. Confirmed or probable oropharyngeal candidiasis and odynophagia

and

2. Response to specific antifungal therapy for the treatment of esophagitis.

ORAL/OROPHARYNGEAL CANDIDIASIS, SPECIFY ORAL OR OROPHARYNGEAL AND PSEUDOMEMBRANOUS OR ERYTHEMATOUS

CONFIRMED

1. One of the following case definitions:

62060 Pseudomembranous candidiasis

Clinical Descriptors: White or yellow/creamy spots or plaques that may be located in any part of the oral cavity and can usually be wiped off to reveal an erythematous surface.
Patient reported symptoms: None or possible mild to moderate burning pain.
Patient reported duration: Lesions/symptoms are usually intermittent, but may be long-standing.

62062 Erythematous candidiasis

Clinical Descriptors: Patchy erythema or red areas usually located on the palate and dorsum of the tongue, but occasionally on the buccal mucosa. At times, white spots or plaques of pseudomembranous candidiasis may also be present.
Patient reported symptoms: None or possible mild to moderate burning pain.
Patient reported duration: Lesions/symptoms are usually intermittent, but may be long-standing.

and

2. Positive culture, KOH or histopathology.

PROBABLE

1. One of the following case definitions:

62061 Pseudomembranous candidiasis

Clinical Descriptors: White or yellow/creamy spots or plaques that may be located in any part of the oral cavity and can usually be wiped off to reveal an erythematous surface.
Patient reported symptoms: None or possible mild to moderate burning pain.
Patient reported duration: Lesions/symptoms are usually intermittent, but may be long-standing.

62063 Erythematous candidiasis

Clinical Descriptors: Patchy erythema or red areas usually located on the palate and dorsum of the tongue, but occasionally on the buccal mucosa. At times, white spots or plaques of pseudomembranous candidiasis may also be present.
Patient reported symptoms: None or possible mild to moderate burning pain.
Patient reported duration: Lesions/symptoms are usually intermittent, but may be long-standing.

and

2. Specific antifungal therapy initiated or recommended.

VULVOVAGINAL CANDIDIASIS

62070 CONFIRMED

1. Compatible clinical syndrome, consisting of one or more signs or symptoms as follows: vulvovaginal pruritus, irritation/soreness or dyspareunia; mucous membrane erythema, white plaques/exudates adherent to vaginal mucosa or thick, curdy vaginal discharge.

and

2. Positive culture or KOH.

62071 PROBABLE

1. Compatible clinical syndrome, consisting of two or more signs or symptoms as follows: vulvovaginal pruritus, irritation/soreness or dyspareunia; mucous membrane erythema, white plaques/exudates adherent to vaginal mucosa or thick, curdy vaginal discharge

and

2. Specific antifungal therapy initiated or recommended.

OTHER CANDIDIASIS

62099

This includes disseminated candidemia and invasive candidiasis.

DISSEMINATED COCCIDIOIDOMYCOSIS

62041 CONFIRMED

Identification of the fungal organism C. immitis by:

a. Positive culture.

or

b. Positive histopathology: identification of characteristic appearance of organism within body tissue or fluids.

PROBABLE

There is no acceptable definition to be used within the ACTG.

COCCIDIOIDAL MENINGITIS (PROBABLE ONLY)

62044 PROBABLE

1. Positive complement fixation serology

and

2. Compatible clinical syndrome consisting of CSF lymphocytic pleocytosis, fever and one or more of the following signs and symptoms of meningitis: headache, altered mental status, stiff neck, and/or photophobia, seizures, and/or focal deficits

and

3. Specific antifungal therapy initiated or recommended.

62045

Clinical diagnosis only, compatible clinical syndrome consisting of CSF lymphocytic pleocytosis, fever and one or more of the following signs and symptoms of meningitis: headache, altered mental status, stiff neck, and/or photophobia, seizures, and/or focal deficits and specific antifungal therapy initiated or recommended.

CRYPTOCOCCAL MENINGITIS

62023 CONFIRMED

1. Identification of cryptococcus in CSF or CNS tissue by:
   a. Positive culture
   or
   b. Histopathology of cryptococcal organisms.

or

2. Compatible clinical syndrome including fever, and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/or focal deficits.

and

3. Positive CSF cryptococcal antigens and/or CSF India Ink preparation.

62024 PROBABLE

1. Compatible clinical syndrome including fever, and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/or focal deficits.

and

2. Positive serum cryptococcal antigen.

and

3. Specific antifungal therapy initiated or recommended.

62025

Clinical diagnosis only, compatible clinical syndrome including fever, and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/or focal deficits and specific antifungal therapy initiated or recommended with treatment response.

DISSEMINATED CRYPTOCOCCOSIS

62020 CONFIRMED

Identification of the fungal organism C. neoformans by:

a. Positive culture.

or

b. Positive histopathology: Identification of characteristic appearance of organism within body tissue or fluids.

62021 PROBABLE

1. Compatible clinical syndrome consisting of fever > 38°C.

and

2. Detection of positive cryptococcal serum antigen ≥ 1:8.

and

3. Specific antifungal therapy initiated or recommended.

PARACOCCIDIOIDOMYCOSIS

62014 CONFIRMED

1. Fever and advanced immunosuppression (CD4 <200 cells/mL)

and

2. Positive culture for P. brasiliensis from sputum, bronchoalveolar lavage, cerebrospinal fluid lymph nodes, lung tissue, skin or any other tissue.

62015 PROBABLE

1. Clinical signs of lung, mucous, skin or lymph node involvement and fever

or

2. New infiltrates on thorax CT imaging or chest X-ray.

and

3. Observation of the characteristic "pilot wheel" shape of P. brasiliensis by direct examination of sputum of bronchoalveolar lavage (KOH prep), or by silver stain of tissue or sputum.

DISSEMINATED HISTOPLASMOSIS

62031 CONFIRMED

Identification of the fungal organism H. capsulatum by:

a. Positive culture.

or

b. Positive histopathology: Identification of characteristic appearance of organism within body tissue or fluids.

62032 PROBABLE

1. Compatible clinical syndrome consisting of one or more signs or symptoms as follows: anemia, leukopenia, thrombocytopenia, elevated alkaline phosphatase, ALT, LDH, or bilirubin, enlarged lymph nodes, spleen and/or liver, skin lesions or gastrointestinal ulcers.

and

2. Detection of positive histoplasma antigen > 1 unit obtained from body fluid.

and

3. Specific antifungal therapy initiated or recommended.

PULMONARY HISTOPLASMOSIS, BLASTOMYCOSIS, COCCIDIOIDOMYCOSIS OR CRYPTOCOCCOSIS

[Since these diagnoses are not AIDS-defining there is no distinction between confirmed and probable.]

62027 PULMONARY CRYPTOCOCCOSIS
62034 PULMONARY HISTOPLASMOSIS
62043 PULMONARY COCCIDIOIDOMYCOSIS
62053 PULMONARY BLASTOMYCOSIS

1. Abnormal chest X-ray or CT scan.

and

2. Either:
    a. Positive histopathology of lung tissue or culture of lung tissue, sputum or BAL of:
        C. neoformans (cryptococcosis)
        H. capsulatum (histoplasmosis)
        C. immitis (coccidioidomycosis)
        B. dermatitidis (blastomycosis)

    or:

    b. Detection of one of the following:
        Histoplasma antigen (>1 unit) in serum, urine, BAL or sputum
        Coccidioidal positive complement fixation titer
        Cryptococcal serum antigen ≥1:8 or other antibody test

and

3. No evidence of extrapulmonary infection.

MOLD INFECTIONS, SPECIFY SPECIES (e.g. aspergillus species, mucormycosis and others)

62197 CONFIRMED

1. Evidence of invasive disease on histopathology.

and

2. Positive culture.

and

3. One of the following:
    a. Compatible clinical syndrome consistent with signs and symptoms of pulmonary fungal infection.

    or

    b. Localized clinical syndrome in sinus, nose, orbit or ear consisting of any of the following: pain, headache, nasal or ear discharge, changes in vision or hearing, facial tenderness, ulceration or necrotic membrane in nose or face, perforation of tympanic membrane, ocular paralysis, otitis externa or media, or radiographic evidence of sinus opacity or bony erosion.

    or

    c. Compatible clinical syndrome consistent with signs and symptoms of skin or soft tissue infection, osteomyelitis, cerebral abscess or meningitis or other organ disease.

62198 PROBABLE

1. Either:
    a. Positive histopathology, cytology or KOH prep from tissue.

    or:

    b. Positive culture.

and

2. One of the following:
    c. Compatible clinical syndrome consistent with signs and symptoms of pulmonary fungal infection.

    or

    d. Localized clinical syndrome in sinus, nose, orbit or ear consisting of any of the following: pain, headache, nasal or ear discharge, changes in vision or hearing, facial tenderness, ulceration or necrotic membrane in nose or face, perforation of tympanic membrane, ocular paralysis, otitis externa or media, or radiographic evidence of sinus opacity or bony erosion.

    or

    e. Compatible clinical syndrome consistent with signs and symptoms of skin or soft tissue infection, osteomyelitis, cerebral abscess or meningitis or other organ disease.

and

3. Specific antifungal therapy initiated or recommended.

FUNGAL NAIL INFECTIONS

62196 CONFIRMED

1. Fungal culture of the nail or nail plate material.

62195 PROBABLE

1. Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration- especially involving proximal part of nail plate- with thickening and separation of the nail from the nail bed).

PENICILLIOSIS MARNEFFEI, DISSEMINATED

62180 CONFIRMED

Isolation of Penicillium marneffei from blood, bone marrow, tissue, or other normally sterile body fluids.

62181 PROBABLE

One of the following major criteria:

1. A finding of elongated yeast like organism with clear central septum in Wright's-stained skin biopsy touch smear or scraping of a skin lesion.

and

At least two of the following minor criteria:

2. Fever, weight loss, papulonecrotic skin lesions, lymphadenopathy, hepatomegaly, splenomegaly, anemia, leukopenia, and thrombocytopenia.

OTHER FUNGI

62997 CONFIRMED

1. Histologic evidence of invasive disease.

and

2. Positive culture or smear from a sterile tissue site.

and

3. Compatible clinical syndrome.

62998 PROBABLE

1. Compatible clinical syndrome.

and

2. Positive culture or smear from a non-sterile site.

and

3. Specific antifungal treatment initiated or recommended.

III. BACTERIAL/MYCOBACTERIAL INFECTIONS

BACTERIAL INFECTION OF DEEP TISSUE, BODY CAVITY OR OTHER NORMALLY STERILE SITE, SPECIFY SITE

65686 CONFIRMED

This category includes, for example, organ parenchymal, deep soft tissue (including pyomyositis) or abdominal abscesses, empyema, purulent pericarditis, meningitis and bone and joint infections.

Demonstration of bacterial pathogen(s) in deep tissue, viscera, body cavity, or other normally sterile site by one of the following methods:

a. Isolation of a bacterial pathogen(s) from an aspirate or biopsy specimen.
b. Appropriate histopathology stain of a specimen.
c. Demonstration of bacterial pathogen(s) by appropriate Gram or microbiological stain of aspirate or biopsy specimen.

65687 PROBABLE

1. Evidence of an infection in a deep tissue, body cavity or other normally sterile site demonstrated by appropriate diagnostic sampling or imaging procedures such as fluid aspiration, biopsy, computerized tomography, ultrasonography, magnetic resonance imaging, radioisotope scanning or plain radiograph.

and

2. Clinical signs and symptoms compatible with the infection.

and

3. Appropriate treatment initiated and response demonstrated. (Appropriate treatment may include drainage procedures and/or antibacterial therapy.)

CATHETER EXIT SITE AND/OR TUNNEL INFECTION

65401 CONFIRMED

1. Erythema, tenderness, induration and/or purulent drainage along the subcutaneous tract or at the skin exit site.

and

2. At least one of the following:
    a. Isolation of a bacterial pathogen(s) from the exit site, tunnel and/or catheter tip.
    b. Appropriate antibacterial therapy is initiated or recommended.

PROBABLE

There is no acceptable definition to be used within the ACTG.

ACUTE GASTROINTESTINAL/DIARRHEAL SYNDROME, Specify
When completing the form specify either acute gastrointestinal syndrome or acute diarrheal syndrome

65001 CONFIRMED

1. Clinical syndrome with acute onset of 3 or more bowel movements (or stools) in a 24 hour period
and
2. Duration lasting greater than or equal to (≥) 3 days and less than or equal to (≤) 14 days.
and
3. Pathogen identified

65002 PROBABLE

1. Clinical syndrome with acute onset of 3 or more bowel movements (or stools) in a 24 hour period
and
4. Duration lasting greater than or equal to (≥) 3 days and less than or equal to (≤) 14 days.
and
2. No pathogen identified

CHRONIC DIARRHEA

65005 CONFIRMED

1. Clinical syndrome of 3 or more bowel movements (or stools) in a 24 hour period.
and
2. Duration greater than or equal to (≥) 28 days
and
3. Pathogen identified

65006 PROBABLE

1. Clinical syndrome of 3 or more bowel movements (or stools) in a 24-hour period.
and
2. Duration greater than or equal to (≥) 28 days
and
3. Either diagnostic testing was done and no pathogen was identified or diagnostic testing was not available.

PERSISTENT DIARRHEA

65007

1. Three (3) or more bowel movements (or stools) in a 24 hour period.
and
2. Duration greater than (>) 14 to less than (<) 28 days.

ACUTE DYSENTERY

65003 CONFIRMED

1. Clinical syndrome with acute onset of 3 or more bowel movements (or stools) in a 24 hour period.

and

2. Visible blood in the stool

and

3. Duration lasting less than or equal to (≤) 14 days

and

4. Pathogen identified

65004 PROBABLE

1. Clinical syndrome with acute onset of 3 or more bowel movements (or stools) in a 24 hour period.

and

2. Visible blood in the stool

and

3. Duration lasting less than or equal to (≤) 14 days

and

4. No pathogen identified

BACTERIAL ENDOCARDITIS

65424 CONFIRMED

1. Persistently positive blood cultures (at least two sets of blood cultures obtained on separate occasions, with either two of four positive cultures, three of six positive cultures, or at least 70% of cultures positive, if four or more sets of blood cultures were obtained.)

and

2. Demonstration of a bacterial pathogen(s) by Gram stain, other histologic stain or culture of valvular vegetation or endocardial tissue.

65425 PROBABLE (A OR B)

EITHER A:

1. Persistently positive blood cultures (at least two sets of blood cultures obtained on separate occasions, with either two of four positive cultures, three of six positive cultures, or at least 70% of cultures positive, if four or more sets of blood cultures were obtained.)

and

2. At least one of the following:
    a. New murmur by physical examination.
    b. Echocardiographic (or other imaging procedure) demonstration of valvular vegetation(s).
    c. Evidence of distal embolus (e.g. petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, hematuria with active urine sediment consistent with glomerulonephritis, or embolic phenomena.)
    d. Septic pulmonary emboli.

and

3. Specific antibacterial therapy initiated or recommended.

OR B:

1. Negative or intermittently positive blood cultures.

and

2. At least three of the following:
    a. Fever greater than (>) 38°C.
    b. New murmur by physical examination.
    c. Evidence of distal embolus (e.g. petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, hematuria with active urine sediment consistent with glomerulonephritis, or embolic phenomena.)
    d. Echocardiographic (or other imaging procedure) demonstration of valvular vegetation(s).
    e. Demonstration of a bacterial pathogen(s) by Gram stain, other histologic stain or culture of peripheral embolus obtained by biopsy.
    f. Septic pulmonary emboli.

and

3. Specific antibacterial therapy initiated or recommended.

HANSEN'S DISEASE/LEPROSY

63031 CONFIRMED

1. Appropriate clinical setting with characteristic dermatological and/or neurological manifestations with consistent histopathology:
   Multibacillary leprosy: Acid fast bacilli seen on the smear
   Paucibacillary leprosy: Well formed non-caseating granuloma and nerve involvement (AFB need not be seen).

63030 PROBABLE

1. Characteristic infiltrative skin lesion, hypoesthesia, or peripheral neuropathy in the appropriate clinical setting.

MYCOBACTERIUM AVIUM COMPLEX (MAC)

63018 CONFIRMED

MAC identified from a normally sterile site (blood, bone marrow, lymph node, liver, cerebrospinal fluid or other normally sterile body fluid, tissue or organ). Conventional (e.g., culture) and DNA probe technologies are acceptable for identification of MAC from cultures.

63019 PROBABLE

1. MAC identified from bronchopulmonary, gastrointestinal, skin surface or other non-sterile site(s) (as the only pathogen) coupled with histopathologic confirmation of AFB/MAC in tissue specimen(s) from which MAC was identified. Conventional (e.g., culture) and DNA probe technologies are acceptable for identification of MAC from cultures.

and

2. A clinical MAC syndrome consisting of one or more of the following: persistent fever greater than or equal to (≥) 38°C for more than one week, night sweats, diarrhea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, anemia (hemoglobin less than (<) 8.5 gm/dL), and alkaline phosphatase elevated to greater than twice the upper limit of normal (72 x ULN).

and

3. Treatment initiated or recommended for MAC

MYCOBACTERIAL INFECTION, OTHER NON-TUBERCULOUS, NON-MAC

CONFIRMED
63021 CONFIRMED, *M. kansasii*
63023 CONFIRMED, *M. genovensii*
63027 CONFIRMED*, other non-MAC, non-TB mycobacteria*

1. Other mycobacterial species cultured from blood, bone marrow, lymph node, liver, cerebrospinal fluid, or any other normally sterile body fluid, tissue or organ.

PROBABLE
63022 PROBABLE, *M. kansasii*
63024 PROBABLE, *M. genovensii*
63028 PROBABLE, OTHER *other non-MAC, non-TB mycobacteria*

1. Other mycobacterial species cultured from bronchopulmonary, gastrointestinal, urine, skin surface or other non-sterile site(s).

and

2. Clinical symptoms, signs, or radiograph/laboratory abnormalities compatible with mycobacterial infection consisting of one or more of the following: persistent fever greater than or equal to (≥) 38°C for more than one week, night sweats, diarrhea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, anemia (hemoglobin less than (<) 8.5 gm/dL), and alkaline phosphatase elevated to greater than twice the upper limit of normal (ULN).

and

3. No alternative pathogen(s) identified or symptoms/signs persist after treatment for and/or elimination of alternative pathogen(s).

and

4. Treatment initiated or recommended for non-tuberculous, non-MAC mycobacteria.

63029

Clinical diagnosis only, clinical symptoms, signs, or radiograph/laboratory abnormalities compatible with mycobacterial infection consisting of one or more of the following: persistent fever greater than or equal to (≥) 38˚C for more than one week, night sweats, diarrhea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, anemia (hemoglobin less than (<) 8.5 gm/dL), and alkaline phosphatase elevated to greater than twice the upper limit of normal and no alternative pathogen(s) identified or symptoms/signs persist after treatment for and/or elimination of alternative pathogen(s) and treatment initiated or recommended for non-tuberculous, non-MAC mycobacteria.

OSTEOMYELITIS

61300 CONFIRMED

Specific test on blood or bone or by histology. Specify bone(s) involved and pathogen(s) identified.

61302 PROBABLE

Suspected clinically and radiologically, negative or no specific test on blood and/or bone. Specify bone(s) involved.

PELVIC INFLAMMATORY DISEASE

69606 CONFIRMED

1. Evidence of purulent material in the peritoneal cavity by culdocentesis or laparoscopic examination.

or

2. Endometrial biopsy findings consistent with acute endometrial infection.

or

3.
    a. Examination elicits cervical motion, adnexal, and/or uterine tenderness.

    and

    b. At least one of the following:
        i. Pelvic abscess or inflammatory complex (tubo-ovarian abscess.)
        ii. Evidence of cervical infection with N. gonorrhea or C. trachomatis.
        iii. Purulent cervical discharge.

69607 PROBABLE

1. Examination elicits cervical motion, adnexal, and/or uterine tenderness.

and

2. At least one of the following:
    a. Temperature greater than 38°C.
    b. Bimanual exam detects pelvic mass consistent with pelvic abscess or inflammatory complex (tubo-ovarian abscess.)
    c. Microscopic examination of the wet mount demonstrating markedly increased numbers of inflammatory cells.

and

3. Treatment initiated or recommended.

69608

Clinical diagnosis only, testing technology not available to determine diagnosis.

BACTERIAL PNEUMONIA

65100 CONFIRMED

1. Chest radiographic examination shows new or progressive infiltrate, consolidation or cavitation.

and

2. At least one of the following:
    a. Bacterial organism(s) cultured from blood with no alternative site of infection.
    b. Isolation of a bacterial pathogen(s) from a culture specimen obtained by transtracheal aspirate, protected bronchial brushing or biopsy.
    c. Histopathologic evidence of pneumonia with bacterial organism(s) demonstrated by Gram stain or culture of tissue specimen or positive Quellung test for pneumococcus.
    d. Demonstration of a predominant bacterial organism by positive culture or Gram stain of an adequate sputum specimen (fewer than 10 epithelial cells and greater than (>) 25 PMNs per high power field).
    e. Fluorescent antibody or other antigen detection method positive for Legionella, Chlamydia or Mycoplasma spp. And no other pathogen identified.

65101 PROBABLE

1. Chest radiographic examination shows new or progressive infiltrate, consolidation or cavitation.

and

2. At least one of the following:
    a. Fever and/or cough.
    b. New onset of purulent sputum or change in character of sputum.
    c. Appropriately collected (acute and convalescent) serologic tests positive for Legionella, Chlamydia or Mycoplasma and no other pathogen identified.

and

1. Appropriate antibacterial therapy initiated or recommended.

65102

Clinical diagnosis only; including history/examination and improvement with antibacterial therapy.

BACTERIAL SEPSIS/CATHETER RELATED BACTEREMIA/SEPSIS

65200 CONFIRMED
BACTERIAL SEPSIS

NOTE: These criteria apply only to bloodstream infections that are unrelated to infection at another site. See criteria for bacterial endocarditis and catheter related sepsis as necessary.

Laboratory-confirmed bloodstream infection must meet at least one of the following criteria:

1. A recognized bacterial pathogen(s) isolated from one or more blood cultures.

or

2. Both:
    a. The presence of at least one of the following signs or symptoms: fever greater than (>) 38°C, chills/rigors or hypotension (systolic pressure greater than or equal to (≤) 90 mm Hg).

    and

    b. Common skin flora (e.g. diphtheroids, coagulase-negative staphylococci, Bacillus spp., proprionibacterium spp., or micrococci) isolated from two or more blood cultures drawn on separate occasions.

CATHETER RELATED BACTEREMIA/SEPSIS

1. Isolation of a known bacterial pathogen(s) from a blood culture in a study participant with an indwelling intravascular catheter and no other alternative site of infection.

or

2. All of the following:
    a. The presence of at least one of the following signs or symptoms: fever greater than (>) 38°C, chills/rigors or hypotension (systolic pressure greater than or equal to (≤) 90 mm Hg).

    and

    b. Common skin flora (e.g. diphtheroids, coagulase-negative staphylococci, Bacillus spp., Proprionibacterium spp., or micrococci) isolated from two or more blood cultures drawn on separate occasions from a study participant with an indwelling catheter.

    and

    c. No other alternative site of infection.

65201 PROBABLE
BACTERIAL SEPSIS
NOTE: These criteria apply only to bloodstream infections that are unrelated to infection at another site. See criteria for bacterial endocarditis and catheter related sepsis as necessary.

1. The presence of at least one of the following signs or symptoms: fever > 38°C, chills/rigors or hypotension (systolic pressure ≤ 90 mm Hg).

and

2. At least one of the following:
    a. Common skin flora (e.g. diphtheroids, coagulase-negative staphylococci, Bacillus spp., Proprionibacterium spp., or micrococci) isolated from one blood culture.
    b. Positive antigen test on blood (e.g. *Hemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides* or Group B Streptococcus).

and

3. Signs and symptoms and positive laboratory results are not related to an alternative etiology.

and

4. Appropriate antibacterial therapy initiated or recommended.

CATHETER RELATED BACTEREMIA/SEPSIS

1. The presence of at least one of the following signs or symptoms: fever > 38°C, chills/rigors or Hypotension (systolic pressure ≤ 90 mm Hg).

and

2. Common skin flora (e.g. diphtheroids, coagulase-negative staphylococci, Bacillus spp., Proprionibacterium spp., or micrococci) isolated from one blood culture drawn from a study participant with an indwelling catheter.

and

3. Appropriate antibacterial therapy is initiated or recommended.

65202
Clinical diagnosis only, testing technology not available to determine diagnosis.

SALMONELLA SEPSIS (NON-TYPHOID)

65204 CONFIRMED

1. Positive blood culture

65203 PROBABLE

1. Clinical exam

and

2. Stool culture positive

BACTERIAL SINUSITIS

65473 CONFIRMED
EITHER A:

1. Isolation of a bacterial pathogen(s) from specimen(s) obtained by drainage procedure(s) of involved sinus(es).

or

2. Demonstration of PMNs and bacterial organism(s) on Gram stain (or other microbial staining technique) from specimen(s) obtained by drainage procedure(s) of involved sinus(es).

OR B:

1. Acute and/or chronic radiographic changes of one or more sinuses as depicted by plain radiograph, CT or MRI scan.

and

2. Isolation of a bacterial pathogen(s) from one or more blood cultures with either:
    a. no material obtained for cultures by a drainage procedure(s) of involved sinus(es),

    or

    b. specimen obtained yielded no growth and there is no other focus of infection.

65474 PROBABLE
EITHER A:

1. A compatible clinical syndrome consisting of fever > 38°C and one or more of the following:
    a. Nasal congestion.
    b. Postnasal drainage.
    c. Facial pain, tenderness or headache.

and

2. Acute and/or chronic changes of one or more sinuses as depicted by plain radiograph, CT or MRI scan.

and

3. Appropriate antibacterial therapy initiated or recommended.

OR B:

1. A compatible clinical syndrome consisting of fever > 38°C and two or more of the following:
    a. Nasal congestion.
    b. Postnasal drainage.
    c. Facial pain, tenderness or headache.

and

2. Appropriate antibacterial therapy initiated or recommended.

65475

Clinical diagnosis only, testing technology not available to determine diagnosis.

RECURRENT UPPER RESPIRATORY TRACT INFECTIONS

Current event plus one or more in last six-month period.

CONFIRMED
65017 TONSILLITIS
65019 OTITIS MEDIA
65021 PHARYNGITIS

1. Laboratory studies where available, such as culture of suitable body fluid.

PROBABLE
65016 TONSILLITIS
65018 OTITIS MEDIA
65020 PHARYNGITIS

1. Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful, inflamed eardrum (otitis media), or tonsillopharyngitis without features of viral infection (such as coryza or cough).

LATENT TUBERCULOSIS (TB) INFECTION

63016 CONFIRMED

1. Positive PPD defined by greater than or equal to (≥)5 mm induration for HIV-infected persons or other approved tuberculosis screening test.

and

2. No clinical, bacteriologic, or radiographic evidence of active tuberculosis

PULMONARY TUBERCULOSIS (TB)

63007 CONFIRMED

Demonstration of mycobacterium tuberculosis (acid fast bacilli) using the Ziehl Nielson or Auramine stain, a positive culture or any future approved diagnostic technologies in any of the following secretions or tissue samples:

a. Sputum
b. Pleural, pericardial and peritoneal fluid
c. Aspirate of lymph node, cold abscess, joint fluid
d. Cerebrospinal fluid
e. Bone marrow aspirate
f. Stool specimen
g. Gastric lavage
h. Bronchoalveolar lavage fluid
i. Histopathology of tissue from any site where mycobacterium tuberculosis has been identified within granulomatous inflammatory lesions. These usually include inter alia
    i. Lymph node biopsy
    ii. Pleural and peritoneal biopsy
    iii. Liver biopsy
    iv. Bone marrow biopsy

63008 PROBABLE

1. AFB not demonstrable.

or

2. Compatible clinical syndrome of one or more of the following:
    a. Radiologic chest X-ray consistent with pulmonary TB
    b. Fever > 38˚C for more than 2 weeks
    c. Unintentional weight loss of more than 10% of body weight
    d. Night sweats
    e. Positive TB exposure
    f. Absence of another possible diagnosis

and

3. Specific antituberculous therapy initiated.

63005

Clinical diagnosis only. The clinician's judgement that the study participant may have pulmonary TB but above criteria are not fulfilled.

1. A fever of unknown origin or a study participant who is deteriorating and pulmonary TB is considered a possibility and therefore empiric TB treatment is instituted.

and

2. A typical chest radiographic pattern of pulmonary TB but the CONFIRMED or PROBABLE criteria above are not satisfied and the clinician feels active TB is likely.

EXTRA PULMONARY TUBERCULOSIS

63012 CONFIRMED

[Including Miliary (disseminated) tuberculosis]
Positive culture for Mycobacterium tuberculosis from extrapulmonary site.

63013 PROBABLE

[Including Miliary (disseminated) tuberculosis]
1. Positive AFB smear or a positive histopathology from an extrapulmonary site.

and

2. Specific multi-drug antituberculous therapy initiated.

63015

[Including Miliary (disseminated) tuberculosis]
Clinical diagnosis only, one or more of the following signs or symptoms consistent with a clinical syndrome for extra pulmonary TB: fever greater than (>) 38˚C, night sweats, malaise, weight loss and/or adenopathy and specific multi-drug antituberculous therapy initiated.

IV. VIRAL INFECTIONS

CMV COLITIS, ADULT ACTG CRITERIA

64014 CONFIRMED

3. Presence of at least one of the following symptoms: abdominal pain or diarrhea (typically in small volume and associated with mucus and blood).

and

4. Tissue biopsy demonstrating CMV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

64114 PROBABLE

1. Presence of at least one of the following symptoms: abdominal pain or diarrhea (typically in small volume and associated with mucus and blood).

and

2. Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion or ulceration.

and

3. CMV is isolated from the lesion.

and

4. Anti-CMV therapy initiated or recommended.

CMV COLITIS, INTERNATIONAL

64214 CONFIRMED

1. Symptoms: persistent or chronic diarrhea for > 14 days, abdominal pain and fever.

and

2. At least one of the following positive results:
    a. Isolation of CMV from the GI tissue
    b. Detection of CMV antigen
    c. Isolation of CMV DNA

64219 PROBABLE

1. Symptoms: persistent or chronic diarrhea for > 14 days, abdominal pain and fever.

and

2. Colonoscopy report that demonstrates widespread submucosal hemorrhages and diffuse mucosal ulcerations.

CMV ENCEPHALITIS

64017 CONFIRMED

1. Rapidly progressive cognitive impairment, progressive change in mental status or delirium, or signs and symptoms of brain stem injury.

and

2. Detection of viral nucleic acids (e.g. PCR) in CSF or CSF CMV culture positive or brain biopsy demonstrating CMV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

64117 PROBABLE

1. Rapidly progressive cognitive impairment, progressive change in mental status or delirium, or signs and symptoms of brain stem injury.

and

2. MRI or contrast CT scan performed which:
    a. Excludes toxoplasmosis, lymphoma, PML or other intracranial process.

    and

    b. Demonstrates periventricular inflammation or meningeal enhancement.

and

3. Other etiologies ruled out.

and

4. CMV end-organ disease (e.g. retinitis, colitis) present.

and

5. Specific therapy initiated, changed or recommended.

64217

Clinical diagnosis only, rapidly progressive cognitive impairment, progressive change in mental status or delirium, or signs and symptoms of brain stem injury, other etiologies ruled out, CMV end-organ disease (e.g. retinitis, colitis) present and specific therapy initiated, changed or recommended.

CMV ESOPHAGITIS

64012 CONFIRMED

1. Presence of at least one of the following symptoms: retrosternal pain or odynophagia (midline retrosternal discomfort with swallowing).

and

2. Tissue biopsy demonstrating CMV by detection of antigen, viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

64112 PROBABLE

1. Presence of at least one of the following symptoms: retrosternal pain or odynophagia (midline retrosternal discomfort with swallowing.)

and

2. Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion and/or ulceration.

and

3. CMV is isolated from the lesion.

and

4. Anti-CMV therapy initiated or recommended.

64210

Clinical diagnosis only with primary symptom of dysphagia and failure to respond to empiric antifungal therapy within 72 hours after presenting with dysphagia, fever and weight loss or anatomopathological exam with characteristic cytopathic changes.

CMV GASTROENTERITIS

64015 CONFIRMED

1. Presence of abdominal pain.

and

2. Tissue biopsy demonstrating CMV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

64115 PROBABLE

1. Presence of abdominal pain.

and

2. Appropriate visualization procedures (endoscopy) that reveal mucosal erythema, erosion or ulceration.

and

3. CMV is isolated from the lesion.

and

4. Anti-CMV therapy initiated or recommended.

64215

Clinical diagnosis only, testing technology not available to determine diagnosis.

MUCOCUTANEOUS CMV ULCERS

64018 CONFIRMED

1. Direct visualization of oral, vulvovaginal, or perianal ulcers.

and

2. CMV culture of lesion or histologic demonstration of typical CMV cytopathology on biopsy of lesion.

PROBABLE

There is no acceptable definition to be used within the ACTG.

CMV PNEUMONITIS

64011 CONFIRMED

1. Hypoxemia and infiltrates on chest X-ray or CT/MRI scan.

and

2. Tissue biopsy or cells obtained by BAL demonstrating CMV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

and

3. No other pathogens identified by routine testing *or* signs/symptoms persist or recur after treatment of copathogens.

64111 PROBABLE

1. Hypoxemia and infiltrates on chest X-ray or CT/MRI scan.

and

2. Positive culture, detection of viral antigen, or detection of viral nucleic acids (e.g. PCR) of CMV from fluid obtained by BAL.

and

3. No other pathogens identified by routine testing *or* signs/symptoms persist or recur after treatment of copathogens.

and

4. Specific antiviral treatment initiated or recommended.

64211

Clinical diagnosis only, testing technology not available to determine diagnosis.

CMV PROCTITIS

64016 CONFIRMED

1. Presence of rectal pain often associated with tenesmus, mucus and blood.

and

2. Tissue biopsy demonstrating CMV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

64116 PROBABLE

1. Presence of rectal pain often associated with tenesmus, mucus and blood.

and

2. Appropriate visualization procedures (endoscopy) that reveal mucosal erythema, erosion or ulceration.

and

3. CMV is isolated from the lesion.

and

4. Anti-CMV therapy initiated or recommended.

64216

Clinical diagnosis only, testing technology not available to determine diagnosis.

CMV RETINITIS

64013 CONFIRMED

Typical lesions including white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages. Lesion(s) has/have irregular, dry-appearing granular border, with little or no overlying vitreous inflammation. Must be diagnosed by an experienced ophthalmologist using indirect ophthalmoscopy and documented by retinal photography that can be independently verified.

64113 PROBABLE

Typical lesions including white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages. Lesion(s) has/have irregular, dry-appearing granular border, with little or no overlying vitreous inflammation. Must be diagnosed by an experienced ophthalmologist using indirect ophthalmoscopy, but is not documented by retinal photographs.

64213

Clinical diagnosis only, history and endoscopic appearance suggestive of CMV disease.

OTHER CMV SYNDROMES, SPECIFY

64019 CONFIRMED (this includes but is not limited to the following)
Hepatitis or cholangitis:

1. ALT or alkaline phosphatase significantly elevated above the study participant's baseline values.

and

2. Tissue biopsy demonstrating CMV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

Radiculomyelopathy:

1. Clinical presentation compatible with CMV end-organ disease, including all of the following:
   a. Decreased lower extremity strength and reflexes or syndrome consistent with a cord lesion present subacutely (over days to weeks).
   b. Myelogram or MRI reveals no mass lesions but lower spinal nerve roots thickened.
   c. CMV positive culture in CSF *or* detection of CMV viral nucleic acids (e.g. PCR) in CSF.

PROBABLE
There is no acceptable definition to be used within the ACTG.

EPSTEIN BARR VIRUS (EBV)

66380 CONFIRMED
Infection (infectious mononucleosis), proven by EBV serology (monospot not acceptable).

66381 PROBABLE
Positive monospot only.

ACUTE HEPATITIS

64066 CONFIRMED

1. Hepatic inflammation diagnosed within 6 months of having a known normal (asymptomatic) liver or chronic stable hepatitis.

   Hepatic inflammation is defined by:
   a) aminotransferase elevation of at least 5 X ULN

   and/or

   b) seropositive for IgM antibody to HAV (acute hepatitis A) or IgM antibody to HBc with presence of new HBsAg (acute hepatitis B) or evidence of HCV viremia without HCV antibody or documented seroconversion within 6 months to anti-HCV with an aminotransferase elevation above the normal level (acute Hepatitis C).

CHRONIC HEPATITIS B

64060 CONFIRMED

Confirmed Chronic Replicative Hepatitis B

1. Hepatitis B surface antigen (Hb_sAg) detected 6 or more months ago.

and

2. Hepatitis B virus DNA (HBV DNA) *or* a Hepatitis B e antigen (Hb_eAg) is detected 6 or more months after the initial detectable Hepatitis B surface antigen (Hb_sAg).

Confirmed Chronic Non-Replicative Hepatitis B

1. Hepatitis B surface antigen (Hb_sAg) detected by repeat testing performed 6 or more months after the initial detectable Hepatitis B surface antigen (Hb_sAg).

and

2. Tests for Hepatitis B virus DNA (HBV DNA) *and* Hepatitis B e antigen (Hb_eAg) are negative 6 or more months after the initial Hb_sAg.

64061 PROBABLE

Probable Chronic Replicative Hepatitis B

1. A Hepatitis B surface antigen (Hb_sAg) detected on two occasions at least 6 months apart.

and

2. Anticore antibody (Anti-Hb_cAB) test positive for either IgG alone or for total antibodies (IgG detectable and IgM not detectable).

64062

Clinical diagnosis only, testing technology not available to determine diagnosis.

CHRONIC HEPATITIS C

64063 CONFIRMED

1. Hepatitis C infection documented 6 or more months ago by HCV ELISA (confirmed by RIBA or PCR) or HCV RNA.

and

2. HCV ELISA or HCV RNA is detectable 6 or more months after the initial testing noted above.

64064 PROBABLE

1. ALT (SGPT) results greater than the upper limit of normal (ULN) on two or more occasions at least 6 months apart.

and

2. Hepatitis C infection detected any time by HCV ELISA (confirmed by RIBA or PCR) or HCV RNA.

64065

Clinical diagnosis only, testing technology not available to determine diagnosis.

HHV6/ROSEOLA INFANTUM

66481

Suspected infection because of clinical diagnosis of roseola, virus detection studies not done or negative.

HSV ESOPHAGITIS

64020 CONFIRMED

1. Presence of at least one of the following symptoms: retrosternal pain or odynophagia (midline retrosternal discomfort with swallowing).

and

2. Tissue biopsy demonstrating HSV by detection of antigen, viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

64021 PROBABLE

1. Presence of at least one of the following symptoms: retrosternal pain or odynophagia (midline retrosternal discomfort with swallowing).

and

2. Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion or ulceration.

and

3. HSV is isolated from the lesion.

and

4. Anti-HSV therapy initiated or recommended.

MUCOCUTANEOUS HERPES SIMPLEX

64023 CONFIRMED

1. Typical (vesicular or ulcerative) HSV lesion(s) in any of the following sites: anogenital (external genitalia, cervix, vagina, perineum, perirectal, rectal), oral, perioral or finger.

and

2. Any one of the following:
    a. HSV isolated from lesion.
    b. HSV antigen detected by immunoassay from vesicular fluid or cells obtained from the base of a vesicle or ulcer.
    c. Recurrence of lesion in same general location: anogenital (external genitalia, cervix, vagina, perineum, perirectal, rectal), oral, perioral or finger with prior documented positive HSV culture.

64024 PROBABLE

1. Clinically apparent typical (vesicular or ulcerative) HSV lesion(s) with prodromal and/or concurrent symptoms of discomfort (burning, itching, pain).

and either 2 or 3:

For an Initial episode:

2. Typical herpes virus inclusions and/or multinucleated giant cells evident in cells obtained from the base of an ulcer or vesicular fluid.

For Recurrence:

3. Specific antiviral treatment initiated or recommended.

64025

Clinically apparent typical (vesicular or ulcerative) HSV lesion(s) with prodromal and/or concurrent symptoms of discomfort (burning, itching, pain) and response to treatment.

HSV PNEUMONITIS

64026 CONFIRMED

1. Hypoxemia and infiltrates on chest X-ray or CT/MRI scan.

and

2. Tissue biopsy or cells obtained by BAL demonstrating HSV by antigen, detection of viral nucleic acids (e.g. PCR) or characteristic cytopathic changes.

and

3. No other pathogens identified by routine testing *or* signs/symptoms persist or recur after treatment of copathogens.

64027 PROBABLE

1. Hypoxemia and infiltrates on chest X-ray or CT/MRI scan.

and

2. Positive culture, detection of viral antigen, or detection of viral nucleic acids of HSV from fluid obtained by BAL.

and

3. No other pathogens identified by routine testing *or* signs/symptoms persist or recur after treatment of copathogens.

and

4. Specific antiviral treatment initiated or recommended.

HERPES LABIALIS

64028

Clinical descriptors: Single or multiple vesicles or ulcers with crusting on vermillion portion of lips and adjacent facial skin.
Patient reported symptoms: Usually mild to moderate pain.
Patient reported duration: Lesion(s) usually present for at most 10-14 days. Prior history of (or recurrent) lesion(s).

RECURRENT INTRA-ORAL HERPES SIMPLEX

64029

Clinical descriptors: Solitary, or cluster of multiple or confluent ulcers that may be noted together with vesicles on keratinized mucosa, including hard palate, attached gingiva and dorsum of tongue. Exceptionally, non-keratinized tissue may be involved. Round to slightly irregular (map-like) margins with minimal to no erythematous halos are present. The base of the ulcers is usually pink. Patient reported symptoms: Usually mild to moderate pain.
Patient reported duration: Lesion(s) usually present for at most 10-14 days. Prior history of (or recurrent) lesion.

MEASLES/RUBEOLA

66500 CONFIRMED
Documented by serology and/or virus detection.

66501 PROBABLE
NOT documented serologically or by virus detection.

MUMPS/PAROTITIS

66862 CONFIRMED
Unilateral or bilateral swelling of the parotid gland with loss of the angle of the mandible, causative agent identified.

66863 PROBABLE
Unilateral or bilateral swelling of the parotid gland with loss of the angle of the mandible, no causative agent identified.

ORAL HAIRY LEUKOPLAKIA

64850 CONFIRMED
Identification of Epstein-Barr virus (EBV) in the epithelial cells of an oral lesion by electron micrograph, in situ hybridization, or immunocytochemistry.

64851 PROBABLE
Clinical descriptors: Whitish/grey lesions on the lateral margins of the tongue. They are not removable and may exhibit vertical corrugations. Lesions range in size as they may be less than one centimeter, or may extend onto the ventral and dorsal surfaces of the tongue where they are usually flat. They may be bilateral or unilateral.
Patient reported symptoms: Asymptomatic
Patient reported duration: Lesion(s) usually long-standing.

64852
Clinical diagnosis only, testing technology not available to determine diagnosis.

ORAL WARTS

64050 CONFIRMED
Characteristic histological appearance on biopsy.

64048 PROBABLE
Clinical descriptors: Mucosal color or white, solitary or multiple (often clustered) raised lesions that range in texture as they may be smooth, spiky, or cauliflower-like, and located in any part of the oral cavity.
Patient reported symptoms: Usually asymptomatic. Note: Warts on the buccal or labial mucosa or tongue may get traumatized by biting, and may be painful.
Patient reported duration: Lesion(s) usually long-standing.

PARVOVIRUS B19

66690
Infection; Fifth disease or aplastic crisis; documented serologically or by PCR.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

64040 CONFIRMED

PML diagnosed by histopathology or in situ hybridization from a brain biopsy or by PCR of cerebrospinal fluid (CSF) for James Canyon Virus (JCV).

64041 PROBABLE

1. Clinical presentation compatible with PML including a subacute or chronic progressive illness with hemiparesis, aphasia, hemianopsia, ataxia and other focal deficits.

and

2. MRI compatible with PML.

64042

Clinical diagnosis only;

1. Clinical presentation consistent with PML including subacute onset of progressive focal neurological abnormalities, including hemiparesis or field cut or ataxia or other abnormality referable to dysfunction of a specific brain region. Does not include cognitive impairment alone.
2. Focal lesions without mass effect or enhancement on CT or MRI of brain.

RUBELLA

66760 CONGENITAL, CONFIRMED, diagnosed clinically with viral detection or serology.

66761 CONGENITAL, PROBABLE, clinical diagnosis**.**

66765 POSTNATAL, documented serologically or by antigen detection or virus isolation.

VARICELLA ZOSTER (VZV, Chickenpox)

64033 VZV, UNCOMPLICATED, primary disease (chickenpox), uncomplicated.

64034 VZV, DISSEMINATED, clinical chickenpox; disseminated disease, including VZV pneumonia, encephalitis, or hepatitis, (with hepatic enzymes greater than 30 times normal).

CUTANEOUS VARICELLA ZOSTER (VZV, Shingles, Herpes Zoster**)**

64030 CONFIRMED
LOCALIZED

1. Painful or dysesthetic lesions appearing in a dermatomal distribution. May be either typical (macular/papular progressing to vesiculopustular) or atypical (ulcerative, necrotic, nodular and/or verrucous).

and

2. Demonstration of VZV in lesions by DFA, culture or PCR.

DISSEMINATED

1. Demonstration of VZV in lesions by DFA, culture or PCR.

and

2. Lesions extend beyond the primary and its adjacent (flanking) dermatomes.

64031 PROBABLE

1. Painful or dysesthetic lesions appearing in a dermatomal distribution.

and

2. Specific antiviral treatment initiated or recommended.

64032

Clinical diagnosis with characteristic rash.

VARICELLA ZOSTER (VZV, SHINGLES, HERPES ZOSTER) WITH VISCERAL DISSEMINATION

64038 CONFIRMED

1. Painful or dysesthetic lesions appearing in a dermatomal distribution. May be either typical (macular/papular progressing to vesiculopustular) or atypical (ulcerative, necrotic, and/or nodular).

and

2. Clinical findings, laboratory test abnormalities and/or radiographic (i.e. X-ray, ultrasonography, CT and/or MRI findings) consistent with the diagnosis.
   Examples:
   a. Pulmonary
      i. Bilateral interstitial infiltrates on chest X-ray and
      ii. Clinical signs and symptoms of pulmonary disease during the course of infection
   b. Hepatitis: Significant elevations of bilirubin, AST, ALT, attributable to VZV
   c. CNS: Encephalopathy and CSF pleocytosis with negative bacterial, acid-fast, fungal and viral cultures (other than HZV)
   d. Myelitis/Paralysis: pain in back or legs, with or without urinary retention, hyperesthesia and motor disturbances or paralysis. Loss or impairment of motor function involves area(s) not within the dermatomal distribution of the study participant's localized zoster.

and

3. Demonstration of VZV in cutaneous or visceral lesions by DFA, culture or PCR.

64039 PROBABLE

1. Painful or dysesthetic lesions appearing in a dermatomal distribution. May be either typical (macular/papular progressing to vesiculopustular) or atypical (ulcerative, necrotic, and/or nodular).

and

2. Clinical findings, laboratory test abnormalities and/or radiographic (i.e. X-ray, ultrasonography, CT and/or MRI findings) consistent with the diagnosis.
   Examples:
   a. Pulmonary
      i. Bilateral interstitial infiltrates on chest X-ray and
      ii. Clinical signs and symptoms of pulmonary disease during the course of infection
   b. Hepatitis: Significant elevations of bilirubin, AST, ALT, attributable to VZV
   c. CNS: Encephalopathy and CSF pleocytosis with negative bacterial, acid-fast, fungal and viral cultures (other than HZV)
   d. Myelitis/Paralysis: pain in back or legs, with or without urinary retention, hyperesthesia and motor disturbances or paralysis. Loss or impairment of motor function involves area(s) not within the dermatomal distribution of the study participant's localized zoster.

V. NEOPLASTIC DISEASES

ADENOCARCINOMA, ENDOCERVICAL

67045 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing endocervical adenocarcinoma.

67030 PROBABLE
Diagnostic cytology or PAP smear results showing endocervical adenocarcinoma.

ADENOCARCINOMA, ENDOMETRIAL

67046 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing endometrial adenocarcinoma.

67031 PROBABLE
Diagnostic cytology or PAP smear results showing endometrial adenocarcinoma.

ADENOCARCINOMA, EXTRAUTERINE

67047 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing extrauterine adenocarcinoma.

67032 PROBABLE
Diagnostic cytology or PAP smear results showing extrauterine adenocarcinoma.

ADENOCARCINOMA, OTHER SITE

67048 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing adenocarcinoma, specify site.

67091 PROBABLE
Diagnostic cytology or PAP smear results showing adenocarcinoma, specify site.

ATROPHY, CERVICAL OR VAGINAL

67036 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing reactive cellular changes associated with atrophy with inflammation ("atrophic vaginitis").

67033 PROBABLE
Diagnostic cytology or PAP smear results showing reactive cellular changes associated with atrophy with inflammation ("atrophic vaginitis").

ATYPIA, GLANDULAR CELL (AGCUS), CERVICAL

67034 CONFIRMED
Diagnostic cytology or PAP smear results showing atypical glandular cells of uncertain significance without intraepithelial neoplasia.

ATYPIA, SQUAMOUS CELL (ASCUS), CERVICAL

67035 CONFIRMED
Diagnostic cytology or PAP smear results showing atypical squamous cells of uncertain significance without intraepithelial neoplasia.

INVASIVE CERVICAL CARCINOMA

66025 CONFIRMED
An abnormal cervical histopathology (biopsy) specimen.

PROBABLE
There is no acceptable definition to be used within the ACTG.

CARCINOMA IN SITU

67044 CONFIRMED (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic histopathology on biopsy or surgical pathology results showing high-grade squamous intraepithelial lesion (HGSIL), carcinoma in situ (CIS).

67080 PROBABLE (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic cytology or PAP smear results showing high-grade squamous intraepithelial lesion (HGSIL), carcinoma in situ (CIS).

CERVICAL INFLAMMATION

67093 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing reactive cellular changes associated with inflammation (including typical repair).

67082 PROBABLE
Diagnostic cytology or PAP smear results showing reactive cellular changes associated with inflammation (including typical repair).

RADIATION CELL CHANGES

67058 CONFIRMED, SPECIFY SITE
Diagnostic histopathology on biopsy or surgical pathology results showing reactive cellular change associated with radiation changes.

67094 PROBABLE, SPECIFY SITE
Diagnostic cytology or PAP smear results showing reactive cellular change associated with radiation changes.

DYSPLASIA

67095 CONFIRMED (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic histopathology on biopsy or surgical pathology (grade unknown).

67083 PROBABLE (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic cytology or PAP smear (grade unknown).

DYSPLASIA/INTRAEPITHELIAL NEOPLASIA, LOW GRADE/GRADE 1

67096 CONFIRMED (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic histopathology on biopsy or surgical pathology results showing low grade squamous intraepithelial neoplasia or dysplasia, specify type.

67084 PROBABLE (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic cytology or PAP smear results showing low grade squamous intraepithelial lesion (LGSIL).

DYSPLASIA/INTRAEPITHELIAL NEOPLASIA, MODERATE/GRADE 2

67097 CONFIRMED (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic histopathology on biopsy or surgical pathology results showing moderate squamous intraepithelial dysplasia or neoplasia, specify type.

67085 PROBABLE (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic cytology or PAP smear results showing high grade squamous intraepithelial lesion (HGSIL), moderate dysplasia.

DYSPLASIA/INTRAEPITHELIAL NEOPLASIA, SEVERE/GRADE 3

67098 CONFIRMED (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic histopathology on biopsy or surgical pathology results showing severe squamous intraepithelial dysplasia or neoplasia.

67086 PROBABLE (Specify site: cervical, vaginal, vulvar, perianal)
Diagnostic cytology or PAP smear results showing high grade squamous intraepithelial lesion (HGSIL), severe dysplasia.

DYSPLASIA/INTRAEPITHELIAL NEOPLASIA/CANCER, VAGINAL

67042 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology, specify type.

67087 PROBABLE
Diagnostic cytology or PAP smear, specify type.

DYSPLASIA/INTRAEPITHELIAL NEOPLASIA/CANCER, VULVAR

67043 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology, specify type.

67088 PROBABLE
Diagnostic cytology or PAP smear, specify type.

IUD REACTIVE CHANGES

67040 CONFIRMED
Diagnostic histopathology on biopsy or surgical pathology results showing reactive cellular changes associated with intrauterine contraceptive device (IUD).

67089 PROBABLE
Diagnostic cytology or PAP smear results showing reactive cellular changes associated with intrauterine contraceptive device (IUD).

KAPOSI SARCOMA (KS) MUCOCUTANEOUS AND VISCERAL

66011 CONFIRMED MUCOCUTANEOUS, specify site
66012 CONFIRMED VISCERAL, specify site
Characteristic histological appearance on biopsy from any site/organ.

66013 PROBABLE MUCOCUTANEOUS, specify site
Characteristic lesion(s) on skin or mucous membrane noted by an experienced physician. The early lesions are typically flat (or macular) with color ranging from red to purple. At a later stage, lesions become nodular, raised and ulcerated.
Oral mucosa descriptors (probable):
Clinical descriptors: Early lesions are typically flat (or macular) with color ranging from red to purple. At a later stage, lesions become nodular, raised and ulcerated. Predominantly seen on the palate or gingiva.
Patient reported symptoms: At early stage, the lesions are asymptomatic. Mild to moderate pain may develop as the lesions become nodular and ulcerated. Local trauma to the more advanced lesions may induce bleeding.
Patient reported duration: Nodular lesions are long-standing.

66014 PROBABLE VISCERAL, specify site
Characteristic lesion(s) on skin or mucous membrane noted by an experienced physician. The early lesions are typically flat (or macular) with color ranging from red to purple. At a later stage, lesions become nodular, raised and ulcerated.

PRIMARY CNS LYMPHOMA (PCL)

66020 CONFIRMED

Positive histopathology/cytology on tissue biopsy of brain or cerebrospinal fluid analysis.

66021 PROBABLE

1. Neurologic signs with CD4 lymphocyte count <100/mm^3

and

2. Mass lesion(s) on head CT/MRI scan.

and

3. Failure of clinical response to antitoxoplasmosis chemotherapy or other anti-infective chemotherapy (e.g. tuberculosis, cryptococcosis).

and

4. Lesion(s) becomes markedly reduced or disappears following high-dose glucocorticoid and/or radiation therapy.

66022

Clinical diagnosis only, testing technology not available to determine diagnosis.

NON-HODGKIN LYMPHOMA (NHL)

CONFIRMED
66031 LYMPHOMA, N-H SMALL NON-CLEAVED (BURKITT OR BURKITT'S LIKE)
66032 LYMPHOMA, N-H IMMUNOBLASTIC
66033 LYMPHOMA, N-H LARGE CELL
66034 N-H INDETERMINATE
66035 LYMPHOMA, ORAL NON-HODGKIN, specify cell type (non-cleaved (Burkitt or Burkitt's like, immunoblastic, large cell or inderteminate)

Including all B cell or indeterminate cell, intermediate to high-grade malignant lymphomas (e.g. large cell, immunoblastic, small non-cleaved, Burkitt or Burkitt's-like lymphoma.) Pathological/biopsy confirmation of NHL is mandatory in all cases.

Positive histopathology/cytology/fine-needle aspiration on tissue biopsy from any site/organ, supported by appropriate immunocytochemical or molecular biological investigations. (Note: bone marrow sampling may confirm diagnosis despite non-diagnostic biopsies from other sites.)

PROBABLE

Oral Non-Hodgkin Lymphoma is the only acceptable probable definition.

66036- LYMPHOMA, ORAL NON-HODGKIN (probable)

Clinical descriptors: A firm elastic, often somewhat reddish swelling, with or without ulceration. The gingiva, palatal mucosa, and fauces are sites of predilection.
(The fauces are the two pillars of mucous membrane, the palatoglossal arch on the anterior and the palatopharyngeal arch on the posterior, surrounding the palatine tonsils.)
Patient reported symptoms: At the early stage, the lesions are usually asymptomatic. Moderate to severe pain may develop as the lesions become ulcerated.
Patient reported duration: Ulcerated lesions and swelling are long-standing.

PREINVASIVE ANOGENITAL NEOPLASIA, SPECIFY SITE

66026 CONFIRMED

1. Characteristic lesion(s) evident on gross examination by cervical or anal microscopy of the vulva, vagina, cervix, perineum, perianal or anal area *or* cytopathology (PAP smear, cervical or anal) showing dysplastic cells.

and

2. Histopathologic (biopsy) examination confirming the presence of dysplasia

66027 PROBABLE

1. Characteristic lesion(s) evident on gross examination by cervical or anal microscopy of the vulva, vagina, cervix, perineum, perianal or anal area *or* cytopathology (PAP smear, cervical or anal) showing dysplastic cells.

and

2. The presence of human papilloma virus (HPV) confirmed by hybrid capture, polymerase chain reaction (PCR) or other testing methods for HPV.

66028

Clinical diagnosis only, testing technology not available to determine diagnosis. Specify site.

NEOPLASM, GYNECOLOGICAL

67049 CONFIRMED

Diagnostic histopathology on biopsy or surgical pathology results showing other malignant neoplasms (specify neoplasm).

67090 PROBABLE

Diagnostic cytology or PAP smear results showing other malignant neoplasms (specify neoplasm).

POLYP

67057 PROBABLE, SPECIFY SITE

Origin uncertain, diagnostic cytology or PAP smear.

POLYP, CERVICAL

67055 CONFIRMED

Diagnostic histopathology on biopsy or surgical pathology.

POLYP, ENDOMETRIAL

67056 CONFIRMED

Diagnostic histopathology on biopsy or surgical pathology.

MALIGNANCY

68649

Any newly diagnosed malignancy, except squamous cell cancer of the skin, specify diagnosis.

CERVICAL/ANOGENITAL SQUAMOUS CELL CANCER, INVASIVE

67092 CONFIRMED

Diagnostic histopathology on biopsy or surgical pathology. Specify site.

67081 PROBABLE

Diagnostic cytology or PAP smear. Specify site.

Any newly diagnosed malignancy, except squamous cell cancer of the skin, specify diagnosis.

ORAL SQUAMOUS CELL CARCINOMA

66015 CONFIRMED

1. Characteristic histological appearance on biopsy.

66016 PROBABLE

Clinical descriptors: Non-healing ulcer with rolled borders or margins. An advanced stage ulcer may be indurated or located on a firm mass.

Patient reported symptoms: At early stage, lesions are usually asymptomatic. Moderate to severe pain may develop as lesions enlarge and become ulcerated.

Patient reported durations: Ulcerated lesions and swellings are long-standing.

VI. PERINATAL/GYNECOLOGIC CONDITIONS

THERAPEUTIC ABORTION, (ELECTIVE/INDUCED)

68138

Termination of pregnancy prior to viability utilizing a medical or surgical procedure.

SPONTANEOUS ABORTION/MISCARRIAGE

68137

Loss of a pregnancy at < 20 weeks gestation either spontaneously or through medical or surgical procedure after documentation of no fetal heart activity.

VAGINAL BLEEDING

68050 VAGINAL BLEEDING <28 WEEKS

Any vaginal bleeding occurring during pregnancy prior to 28 weeks gestation and prior to the onset of labor.

68052 VAGINAL BLEEDING ≥ 28 WEEKS

Any vaginal bleeding occurring during pregnancy at or after 28 weeks gestation and prior to the onset of labor.

CHORIOAMNIONITIS/AMNIOTIC FLUID INFECTION

61085 CONFIRMED

Amniotic fluid with a positive gram stain or culture.

61086 PROBABLE

1. Clinical diagnosis by obstetrician alone

or

2. Maternal oral temperature greater than or equal to 100.4º F or 38 º C not attributable to other causes

and any two of the following:

a. Fetal heart rate which is persistently >160BPM
b. Maternal heart rate which is >120BPM in the absence of tocolytics or known maternal heart tachyarrhythmia
c. Uterine tenderness not associated with contractions
d. Purulent cervical discharge or amniotic fluid
e. Premature labor unresponsive to tocolytic therapy

CORD PROLAPSE

68020

Documentation of protrusion of the umbilical cord through the cervical os.

GESTATIONAL DIABETES (MEDICATION DEPENDENT)

68030

1. Abnormal three-hour glucose tolerance test during pregnancy, specify gestational age at diagnosis. Criteria: two abnormal serum values from the following:
    a. Fasting > 95; 1 hour > 180; 2 hour > 155; 3 hour >140
    or
    b. Abnormal 1 hour post 50 gram glucose load of >200 mg/dL
    or
    c. 2 abnormal fasting blood sugars according to institutional standards, specify values
    or
    d. Gestational diabetes diagnosed by another method, specify method of diagnosis

and

2. Hyperglycemia requiring the administration of insulin or oral agent and diabetic diet

GESTATIONAL DIABETES (DIET)

68032

1. Abnormal three-hour glucose tolerance test during pregnancy, specify gestational age at diagnosis. Criteria: two abnormal serum values from the following:
    a. Fasting > 95; 1 hour > 180; 2 hour > 155; 3 hour > 140
    or
    b. Abnormal 1 hour post 50 gram glucose load of >200 mg/dL
    or
    c. 2 abnormal fasting blood sugars according to institutional standards, specify values
    or
    d. Gestational diabetes diagnosed by another method, specify method of diagnosis

and

2. Control of hyperglycemia with diabetic diet alone and no history of elevated blood sugar prior to pregnancy.

ECLAMPSIA

68076

1. Seizure during pregnancy in the absence of any underlying known etiology or without any known reason for seizure.

and

2. No suspicion of epilepsy or trauma.

ENDOMETRITIS

61172 CONFIRMED

Etiology proven by positive test for specific organism in endocervical secretions or positive endometrial culture.

61173 PROBABLE

Diagnosed clinically, etiology unproven, maternal postpartum fever greater than or equal to 38° C not attributable to other causes and accompanied by uterine tenderness.

EPISIOTOMY INFECTION, MAJOR

68172

1. Oral temperature ≥100.4˚F or 38˚C in the absence of other sources of fever

and

2. Pus draining/drained from wound *or* wound dehiscence (episiotomy breakdown) requiring debridement.

EPISIOTOMY INFECTION, MINOR

68173

Erythema, edema and tenderness *or* health care provider diagnosis.

FEBRILE MORBIDITY

68039 INTRAPARTUM

Oral, aural/tympanic or forehead temperature ≥100.4º F or 38º C or rectal temperature ≥100º F Or 38.3º C.

68040 POSTPARTUM

Oral, aural/tympanic or forehead temperature ≥100.4º F or 38º C on any two occasions 4 hours apart from >24 hours post delivery through 10 days postpartum.

HELLP SYNDROME (HEMOLYSIS, ELEVATED LIVER ENZYMES, LOW PLATELETS)

68045

This diagnosis should be reviewed by an obstetrician for confirmation before being reported.

1. The diagnosis must be made after 20 weeks gestation.

and

2.
    a. For women with no hypertension or proteinuria before 20 weeks gestation: Pregnancy associated hypertension consisting of a diastolic blood pressure of 90 mmHg or greater on two occasions, 4 hours to 1 week (or 168 hours) apart.

    b. For women with hypertension but no proteinuria before 20 weeks gestation: no hypertension requirement.

    c. For women with proteinuria but no hypertension before 20 weeks gestation: no hypertension requirement.

and

3. All of the following:
    a. Thrombocytopenia: at least one platelet count <100,000 per cubic millimeter (mm^3)
    b. AST/SGOT ≥ 70 U per liter (U/L).
    c. Hemolysis: LDH ≥600 U per liter (U/L) *or* total bilirubin concentration ≥ 2 mg per deciliter (mg/dL) *or* a peripheral smear with nucleated RBCs or schistocytes.

HEMATOMA, VAGINAL OR VULVAR

68060

Documentation of a collection of blood, specify site.

HEMORRHAGE, INTRAPARTUM

68054 HEMORRHAGE WITH HEMODYNAMIC INSTABILITY INTRAPARTUM

1. Bleeding

and

2. Blood pressure <90/60

or

3. Maternal heart rate>120 BPM.

and

4. Includes only those episodes treated with fluid/volume expanders.

68056 HEMORRHAGE REQUIRING SURGICAL PROCEDURE INTRAPARTUM

Bleeding that necessitates surgical intervention, such as dilation and curettage, hysterectomy or uterine artery ligation or embolizaton

68058 HEMORRHAGE REQUIRING TRANSFUSION, INTRAPARTUM

Bleeding with estimated maternal blood loss of > 750 mL in vaginal delivery or >1200 mL in caesarean delivery that necessitates transfusion intrapartum

HEMORRHAGE, POSTPARTUM

68055 HEMORRHAGE WITH HEMODYNAMIC INSTABILITY POSTPARTUM

1. Postpartum maternal hemorrhage with estimated maternal blood loss of >750 mL in vaginal delivery or >1200 mL in caesarean delivery,

and

2. Hemodynamic instability

and

3. BP < 90/60 *or* HR >120 BPM

and

4. Treated with fluid/volume expanders.

68057 HEMORRHAGE REQUIRING SURGICAL PROCEDURE POSTPARTUM

Bleeding with estimated maternal blood loss of >750 mL in vaginal delivery or >1200 mL in caesarean delivery, which requires additional surgery such as dilation and curettage, hysterectomy or uterine artery ligation or embolization to control bleeding. Examples include retained placenta requiring curettage, placenta accreta requiring hysterectomy, and vaginal lacerations requiring repair in an operating room.

68059 HEMORRHAGE REQUIRING TRANSFUSION, POSTPARTUM

Bleeding with estimated maternal blood loss of >750 mL in vaginal delivery or >1200 mL in caesarean delivery that necessitates transfusion to maintain hemodynamic stability as defined by one of the following: to correct BP<90/60 or HR >120 BPM; or to maintain hematocrit >20.

HYPERTENSION, CHRONIC, IN PREGNANCY

68072

Blood pressure persistently ≥140/90 mm Hg that began prior to pregnancy or in the first 20 weeks of pregnancy *or* study participant is on anti-hypertension medication at the onset of pregnancy.

HYPERTENSION, PREGNANCY-INDUCED

68070

Blood pressure persistently ≥ 140/90mm Hg WITHOUT proteinuria and onset after first 20 weeks gestation with no hypertension prior to pregnancy.

INCOMPETENT CERVIX

68082

History consistent with incompetent cervix or current exam by physical diagnosis or imaging study as determined by obstetrician.

INCOMPETENT CERVIX, PROPHYLACTIC CERCLAGE

68080

History consistent with incompetent cervix, resulting in prophylactic cerclage placement.

INCOMPETENT CERVIX, EMERGENCY CERCLAGE

68081

History consistent with incompetent cervix, resulting in emergency cerclage placement.

INTRAUTERINE FETAL DEMISE

68182

Intrauterine death at ≥20 weeks gestational age. Specify gestational age at diagnosis of general death.

INTRAUTERINE GROWTH RESTRICTION (IUGR) FETAL

68090

Based on ultrasound with estimated fetal weight ≤ 10th percentile for gestational age.

INTRAUTERINE GROWTH RESTRICTION (IUGR) FETAL, SEVERE

68091

Based on ultrasound with estimated fetal weight ≤ 3rd percentile for gestational age.

PREMATURE LABOR

68140

Uterine contractions after 20 weeks and before 37 weeks necessitating tocolytic therapy and/or resulting in delivery.

MASTITIS

68100 CONFIRMED

In postpartum study participant.

1. Oral temperature >100.4° Fahrenheit or 38° Celsius.

and

2. Any two of the following:
    a. Unilateral breast (not nipple) pain
    b. Erythema and induration in one area of the breast
    c. Fluctuation of one area of the breast

68101

Clinical diagnosis only by the health care provider.

OLIGOHYDRAMNIOS

68110

Amniotic fluid index (AFI) less than 5 cm or largest vertical pocket <2 cm *or* diagnosis by ultrasound without AFI information.

ABRUPTIO PLACENTA

68010

Examination of the placenta at delivery reveals retroplacental clot *or* clinical diagnosis in study participant with two of the following: vaginal bleeding; uterine tenderness without other evidence of chorioamnionitis; hypercontractility and/or hypertonus.

PLACENTA ACCRETA (TOTAL OR PARTIAL)

68121

Placental villi invasion of the myometrium at the site of implantation and leading to obliteration of the nomal cleavage plane.

PLACENTA INCRETA

68123

Abnormal placental implantation with the villi extending into the myometrium.

PLACENTA PERCRETA

68122

Invasion of villi through the full thickness of the myometrium.

PLACENTA PREVIA

68120

Documentation that the placenta overlies the cervical os by one of the following: by ultrasound; at delivery or at time of caesarean section.

POLYHYDRAMNIOS

68130

Amniotic Fluid Index (AFI) ≥25 cm or maximum vertical pocket > 8 cm *or* diagnosis by ultrasound without AFI information.

PRE-ECLAMPSIA

68074

1. Must occur after 20 weeks of gestation:

and

2. Blood pressure persistently ≥140/90 mm Hg

and at least one of the following:

a. Proteinuria of ≥ 1+ by dipstick, on two occasions

or

b. ≥300mg protein in 24 hour collection

PREGNANCY

68135 ECTOPIC PREGNANCY

Implantation of the fertilized ovum outside the uterine cavity.

68136 INTRAUTERINE PREGNANCY

PREGNANCY, POSTDATES/POST-TERM

68153

Pregnancy at ≥ 42 weeks gestation.

PREMATURE RUPTURE OF MEMBRANES, PRETERM, CONFIRMED

68150

Spontaneous rupture of membranes <37 weeks. Must be documented by *one of the following*:

a. Visualizing a pool of amniotic fluid in the vagina; or
b. Gross leakage of amniotic fluid from the vagina;
c. Positive peri-pad test after installation of indigo carmine dye;
d. Elevated pH;
e. Ferning of dried fluid on a microscope slide;
f. History consistent with premature rupture of membranes or
g. Decreased amniotic fluid volume on ultrasound with no other explanation for the oligohydramnios.

PREMATURE RUPTURE OF MEMBRANES, PROBABLE

68151
Suspected but not confirmed.

PRETERM DELIVERY

68152
Delivery before 37 completed weeks gestation.

UTERINE ATONY

68185
Failure of the uterus to contract postpartum, requiring intervention.

UTERINE INVERSION

68186
Clinical diagnosis by obstetrical provider.

UTERINE RUPTURE

68184
Spontaneous rupture of pregnant uterus resulting in fetal distress, maternal hemorrhage, or extrusion of all or part of the fetus. Does not include asymptomatic uterine dehiscence.

UTERINE SCAR DEHISCENCE

68196
Separation of scar from prior uterine surgery without meeting any of the criteria for uterine rupture, asymptomatic.

ABDOMINAL WOUND INFECTION, MAJOR (CAESAREAN)

68170
1. Oral temperature ≥100.4° F or 38° C in the absence of other source of fever
and
2. Pus draining/drained from wound *or* wound dehiscence requiring debridement.

ABDOMINAL WOUND INFECTION, MINOR (CAESAREAN)

68171
Erythema, edema and tenderness *or* health care provider diagnosis.

VII. NEONATAL DISORDERS (Infants)

HEMOLYTIC DISEASE OF THE NEWBORN

67248 ABO HEMOLYTIC DISEASE OF THE NEWBORN
67249 RH HEMOLYTIC DISEASE OF THE NEWBORN

Mediated by maternal antibody, Coomb's positive.

NEONATAL HEPATITIS

61008
Characterized by elevated transaminases 1.5 times the upper limit of normal with or without clinical findings such as jaundice, hepatomegaly, and hepatic failure.

INTRAVENTRICULAR HEMORRHAGE, GRADE 3, NEONATAL

68190
Radiologic diagnosis of hemorrhage into the germinal matrix tissues of the developing brain with possible rupture into the ventricular system and parenchyma.

INTRAVENTRICULAR HEMORRHAGE, GRADE 4, NEONATAL

68189
Radiologic diagnosis of hemorrhage into the germinal matrix tissues of the developing brain with possible rupture into the ventricular system and parenchyma.

KERNICTERUS

61010
Clinical neonatal syndrome in the presence of severe indirect hyperbilirubinemia (>20mg/dL) associated with CNS symptoms, such as lethargy, hypotonia, irritability, poor Moro response, and poor feeding. Clinical findings include bulging fontanel, opisthotonic posturing, pulmonary hemorrhage, fever, hypertonicity, paralysis, and/or seizures.

MECONIUM ASPIRATION SYNDROME

68192
Aspiration of meconium mixed with amniotic fluid in utero or during delivery causing a partial or complete blockage of the airways associated with poor gas exchange in the lungs and chemical pneumonitis.

NECROTIZING ENTEROCOLITIS, NEONATAL

68193 CONFIRMED
Inflammation causing destruction of part of the bowel, may involve only the innermost lining or the entire thickness of the bowel, variable amounts of the bowel, proven by either surgery or radiographic study.

68194 PROBABLE
Inflammation causing destruction of part of the bowel, may involve only the innermost lining or the entire thickness of the bowel, variable amounts of the bowel: radiographic study non-diagnostic.

RESPIRATORY DISTRESS SYNDROME, NEWBORN

68197
Clinical presentation of respiratory distress in a premature infant due to surfactant deficiency.

NEONATAL SEPSIS

61009
Clinical and/or laboratory findings indicating the presence of disseminated bacterial infection in the infant (0-6 weeks of age).

CONGENITAL SYPHILIS, EARLY

61500 CONFIRMED
< 1 year old, characteristic symptoms; demonstration of T. pallidum in specimens from infant or stillbirth.

61501 PROBABLE
< 1 year old, based on maternal history, infant or maternal serologic findings, and clinical presentation of infant; organism not detected.

CONGENITAL SYPHILIS, LATE, SYMPTOMATIC

61510
Aged > 1 year old; seropositive with clinical evidence of late sequelae of congenital syphilis.

CONGENITAL SYPHILIS, LATE, ASYMPTOMATIC

61511
Asymptomatic, aged > 1 year old; seropositive without clinical evidence of late sequelae of congenital syphilis.

TORCH SYNDROME

63100

Clinical and/or laboratory findings in the neonate indicating one of the following congenital infections: toxoplasmosis, rubella, cytomegalovirus (CMV), or congenital herpes simplex infection (HSV).

TOXOPLASMOSIS, CONGENITAL

65030 CONFIRMED, SYMPTOMATIC

Diagnosed by IgM/IgA serology or histopathology within 1st month of life, with clinical evidence of disease by CT scan, ophthalmologic exam, or physical exam.

65031 PROBABLE, SYMPTOMATIC

Diagnosed by IgM/IgA serology or histopathology at 1-5 months of life, with clinical evidence of disease by CT scan, ophthalmologic exam, or physical exam.

65040 CONFIRMED, ASYMPTOMATIC

Diagnosed by IgM serology or histopathology within 1st month of life, with no symptoms or signs.

65041 PROBABLE, ASYMPTOMATIC

Diagnosed by IgM serology or histopathology within 1-5 months of life, with no symptoms or signs.

TRANSIENT TACHYPNEA, NEWBORN

68198

Noninfectious acute respiratory disease in newborn infants which results in admission to a critical care unit. TTN is the result of a delay in clearance of fetal lung liquid. Signs of respiratory distress (e.g., tachypnea, nasal flaring, grunting, retractions, cyanosis in extreme cases) become evident shortly after birth. The disorder is indeed transient, with resolution occurring usually by age 72 hours.

VIII. BIRTH DEFECTS

69233 ANOMALIES OF THE EAR, congenital, specify anomaly.

69232 ANOMALIES OF THE EYE, congenital, specify anomaly.

69234 ANOMALIES OF THE NOSE, congenital, specify anomaly.

69204 CLEFT LIP
CLEFT PALATE
(If the study participant has both a cleft lip and a cleft palate, report each of these as a separate diagnosis using the same diagnosis code.)

69205 CNS ANATOMICAL DEFECT, other, specify.

69228 CUTANEOUS DEFECTS, specify (e.g., skin dimples, brachial cleft and thyroglossal, supernumery nipples).

69226 DIAPHRAGMATIC HERNIA, hemidiaphragm/absence of diaphragm, congenital**.**

69202 DOWN SYNDROME, Trisomy 21.

69208 ENDOCRINE BIRTH DEFECT, other, specify.

69209 FETAL ALCOHOL SYNDROME

69210 GASTROINTESTINAL, anatomical defect, specify

69212 GENITOURINARY, MALE, anatomical defect, specify**.**

69213 GENITOURINARY, FEMALE, anatomical defect, specify**.**

69214 GENITOURINARY DEFECT, other, specify.

69222 GLYCOGEN STORAGE DISEASE, congenital, specify.

69200 HEART DEFECTS, (anatomical), specify.

69207 INFANT OF DIABETIC MOTHER

69221 INBORN ERRORS OF METABOLISM

69223 MUSCULOSKELETAL ABNORMALITY, congenital, specify**.**

69225 MUSCULOSKELETAL, ABSENCE OF, congenital, specify**.**

69224 MUSCULOSKELETAL DUPLICATION, specify.

69206 NEURAL TUBE DEFECT, includes Spina Bifida, specify defect.

69230 PIGMENT DISORDERS (e.g., albinism, café au lait spots), specify size and location.

69211 PYLORIC STENOSIS, congenital, proven.

69227 RESPIRATORY BIRTH DEFECT, other, specify.

69231 SKIN BIRTH DEFECT, other, specify.

69201 TRISOMIES-TRISOMY, specify.

69203 TURNER SYNDROME

69229 VASCULAR LESIONS (e.g., port wine, nevi and hemangiomas).

69239 OTHER BIRTH DEFECT, specify.

IX. MITOCHONDRIAL DISORDERS

Mitochondrial diseases result from failures of the mitochondria (specialized compartments present in every cell of the body except red blood cells), which are responsible for creating more than 90% of the energy needed by the body to sustain life and support growth. When they fail, less and less energy is generated within the cell. Cell injury and even cell death follow. If this process is repeated throughout the body, whole systems begin to fail, and the life of the person in whom this is happening is severely compromised. These inherited diseases primarily affect children but adult onset may occur.

Diseases of the mitochondria appear to cause the most damage to cells of the brain, heart, liver, skeletal muscles, kidney and the endocrine and respiratory systems.

Depending on which cells are affected, symptoms may include loss of motor control, muscle weakness and pain, gastro-intestinal disorders and swallowing difficulties, poor growth, cardiac disease, liver disease, diabetes, respiratory complications, seizures, visual/hearing problems, lactic acidosis, developmental delays and susceptibility to infection.

Please note that great care is required when applying one of the following diagnoses due to the overlapping of symptoms associated with this particular class of diseases.

ALPER'S DISEASE

69300

Progressive neurodegenerative disease of the brain characterized by developmental delay, progressive mental retardation, hypotonia, spasticity and dementia, seizures often intractable, including epilepsia partialis continua, optic atrophy, and chronic liver dysfunction leading to liver failure.

CYCLIC VOMITING SYNDROME

69301

Childhood disorder; bouts of vomiting that last from a few hours to several days, occurring regularly at intervals of days, weeks or months.

KEARNS-SAYRE SYNDROME (KSS)

69302

Progressive external ophthalmoplegia, retinal pigmentary degeneration, cardiac conduction block, short stature, hearing loss, increased cerebrospinal fluid protein, ataxia, cognitive dysfunction, diabetes, and other endocrine disorders. Caused by large deletions in mitochondrial DNA.

LEIGH SYNDROME (SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY)

69305

Degeneration of the central nervous system. Erratic breathing patterns (cyclic or Cheyne-Stokes) or respiratory failure are common. Brain MRI may show a characteristic pattern of lesions in basal ganglia, thalamus and brainstem, but may also be normal. Autopsy shows characteristic neuropathological changes in similar regions.

Mitochondrial Myopathies:

Muscle weakness or exercise intolerance due to underlying mitochondrial cytopathy. May be accompanied by other organ system disturbance, commonly heart failure or rhythm disturbances, dementia, movement disorders, stroke-like episodes, deafness, blindness, vomiting, and seizures. Ragged red fibers on muscle biopsy, abnormal mitochondria on electron microscopy, and/or documented muscle oxidative phosphoralation defects are necessary to confirm diagnosis.

LEBER PROGRESSIVE OPTIC NEUROPATHY

69304

Delayed bilateral loss of vision which could lead to total blindness due to degeneration of the optic nerve. Early signs include localized collection of distended blood capillary vessels around the start of the optic nerve.

MITOCHONDRIAL DNA DEPLETION/CONGENITAL MYOPATHY

69307

Neonatal weakness, hypotonia requiring assisted ventilation, possible renal dysfunction, severe lactic acidosis, and prominent ragged-red fibers in muscle biopsy.

MITOCHONDRIAL DNA DEPLETION/INFANTILE MYOPATHY

69308

Following normal early development until one year of age, weakness appears and worsens rapidly, causing respiratory failure and death typically within a few years.

MITOCHONDRIAL DNA DEPLETION/HEPATOPATHY

69309

Enlarged liver and intractable liver function, myopathy, and severe lactic acidosis. Death is typical within the first year.

MITOCHONDRIAL ENCEPHALOPATHY LACTIC ACIDOSIS *AND* STROKE-LIKE EPISODES (MELAS)

69310

Stroke-like episodes with focal neurological deficits, lactic acidosis; may also include short stature, seizures, recurrent headaches, cognitive regression.

MYOCLONIC EPILEPSY *AND* RAGGED-RED FIBER MYOPATHY (MERRF)

69311
Myoclonic epilepsy, progressive ataxia, muscle weakness and degeneration, ragged red fibers on biopsy, deafness, and dementia.

NEUROGENIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

69312
Progressive external ophthalmoplegia (abnormal eye movements), progressive proximal muscle weakness, cataracts, ataxia, episodic ketoacidotic coma and episodic ketoacidosis.

NEUROPATHY, ATAXIA *AND* RETINITIS PIGMENTOSA (NARP)

69313
Sensory neuropathy, cerebellar ataxia, retinitis pigmentosa, dementia, seizures, developmental delay, and proximal weakness.

PEARSON'S SYNDROME (PS)

69314
Bone marrow involvement (pancytopenia), and exocrine pancreatic insufficiency. This syndrome is caused by large deletions in mitochondrial DNA.

RENAL FANCONI SYNDROME

69315
Proximal tubular dysfunction, causing excretion of glucose, amino acids, uric acid and phosphate. Secondary growth failure, rickets, and osteomalacia may occur.

69316 MITOCHONDRIAL SYNDROME, not listed above, specify.

X. METABOLIC/ENDOCRINE DISORDERS

ADDISON'S DISEASE

67210

Primary adrenal insufficiency manifested by lassitude, malaise, salt-craving and frequently hyponatremia with hyperkalemia are present on laboratory testing. The diagnosis can be confirmed by the finding of low serum cortisol levels particularly in the early morning, accompanied by high levels of ACTH.

CUSHING'S SYNDROME

67205

Primary overactivity of the adrenal glands or secondary adrenal overactivity due to pituitary hypersecretion of ACTH. The clinical picture can also be seen in study participants on high doses of glucocorticoid medication. The picture is one of central obesity with relatively thin limbs. Fat may accumulate at the base of the neck in a buffalo hump. Characteristic striae or stretch marks may be seen on the upper arms, abdomen or flanks. The face is full. The diagnostic workup is complex and is based initially on a high level of cortisol in a 24 hour urine and high serum cortisol levels especially in the evening and night.

FAILURE TO THRIVE

67200

Based on consecutive weight and height measurements at the same site, documenting measurements from a child who downwardly crosses two major percentile lines on a standard growth chart, or who is less than the 5th percentile and fails to parallel the growth curve at the 5th percentile.

HYPERTHYROIDISM

67212

An autoimmune disorder more common in females than males, which causes excessive amounts of thyroid hormone to be secreted. Symptoms include hyperactivity with a large appetite, feeling hot, with the skin warm to the touch. There may be tremors, excessive sweating, and diarrhea. There is usually goiter or thyroid enlargement. The eyes may be protuberant or staring. Thyroxine values are elevated usually above 12 micrograms/dL. TSH is suppressed.

HYPOTHYROIDISM

67213

Underactivity of the thyroid more common in females than males. Symptoms are weight gain, growth failure, lassitude, constipation and feeling cold. The skin may feel dry to the touch and cold. There may be enlargement of the thyroid. Blood tests showed a reduced thyroxine level usually below 4 micrograms/dL and an elevated TSH.

PRECOCIOUS PUBERTY

67223
The premature development of pubertal changes in a young child.

PREMATURE ADRENARCHE

67224
Appearance of sexual hair before the age of 8 in girls or 9 in boys without evidence of maturation.

PREMATURE THELARCHE

67217
Transient condition of isolated breast development.

SALIVARY GLAND ENLARGEMENT (PAROTID)

67225
Clinical descriptors: enlarged parotid glands, usually bilateral.
Patient reported symptoms: Usually asymptomatic enlargement. Patient may report xerostomia (perception of dry mouth).
Patient reported duration: Usually long standing.

SALIVARY HYPOFUNCTION (HYPOSECRETION)

67226
Defined as unstimulated whole salivary flow rate less than (<)2.5 mL per 5 minutes (0.5mL/min).

67219 METABOLIC/ENDOCRINE DISORDER, other, specify.

XI. NEUROLOGICAL DISORDERS

AUTISM

67305

Disorder characterized by the presence of markedly abnormal or impaired development in social interaction, qualitative impairment in communication and play and a markedly restricted repertoire of activity or interests. The qualitative impairments are distinctly deviant relative to the individual's developmental level or mental age. The disturbance in social interaction, language for social communication, and symbolic play are manifested prior to three years of age.

CHILDHOOD DISINTEGRATIVE DISORDER

67309

Characterized by a marked regression in multiple areas of functioning following a period of at least two years of normal development. After the first two years of life and before age 10, the child has a clinically significant loss of previously acquired skills in at least two of the following areas: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play or motor skills. Individuals with this disorder exhibit the social and communicative deficits and behavioral features observed in autistic disorder; it does not occur in the context of a degenerative disease of the brain or schizophrenia.

68514 CNS DISEASE/DISORDER, other, specify diagnosis

CNS MASS LESION OF UNDETERMINED ETIOLOGY (PROBABLE ONLY)

69920 PROBABLE

1. Presence of mass lesion(s) on brain imaging study (CT or MRI).

and

2. Study participant does not meet all confirmed or probable criteria for other diagnosis with CNS mass lesion (e.g. CNS Toxoplasmosis, CNS Lymphoma).

69921

Clinical diagnosis only, testing technology not available to determine diagnosis.

COMMUNICATION DISORDERS, SPECIFY

67336

Characterized by significant difficulties or lack of development of age appropriate speech and/or language skills. These difficulties interfere with academic or occupational achievement or with social communication and are not due to sensory or motor deficit or environmental deprivation. Communication disorders may include expressive language disorder, mixed receptive-expressive language disorder, phonological disorder, and/or stuttering.

HIV-ASSOCIATED DEMENTIA (ENCEPHALOPATHY)

NOTE: When recording this diagnosis specify either dementia or encephalopathy.

67037 CONFIRMED

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living (verifiable by report of a key informant), not attributable solely to severe systemic illness or medication adverse effects.

and

2. Abnormalities from at least *two* of the following categories:
    a. Motor abnormality: For example, slowed rapid movements, release signs, abnormal gait, limb incoordination, diffuse hyperreflexia, hypertonia, or weakness.
    b. Behavioral abnormality: For example, change in personality with apathy, inertia, irritability, and/or emotional lability or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition.
    c. Cognitive abnormality (two or more): memory, judgment, flexibility, visual, constructional difficulties, reaction time, speed of mental processing, attention and/or concentration as determined by appropriate neuropsychological instruments, with interpretation of abnormality or decline by a neurologist/neuropsychologist.

and

3. No other etiology confirmed by MRI/CT scan, negative CSF cryptococcal antigen or CSF CMV PCR: exclude active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance use or substance withdrawal.

67038 PROBABLE

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living (verifiable by report of a key informant), not attributable solely to severe systemic illness or medication adverse effects.

and

2. Abnormalities from at least two of the following categories:
    a. Motor abnormality: For example, slowed rapid movements, release signs, abnormal gait, limb incoordination, diffuse hyperreflexia, hypertonia, or weakness.
    b. Behavioral abnormality: For example, change in personality with apathy, inertia, irritability, and/or emotional lability or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition.
    c. Cognitive abnormality (two or more): memory, judgment, flexibility, visual, constructional difficulties, reaction time, speed of mental processing, attention and/or concentration as determined by appropriate neuropsychological instruments, with interpretation of abnormality or decline by a neurologist/neuropsychologist.

and

3. Tests for other possible etiology (active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance abuse or substance withdrawal) are not completed, results are not available or results do not exclude other CNS processes.

67039

Clinical diagnosis only, acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living, not attributable solely to severe systemic illness or medication adverse effects and other possible etiologies do not exclude other CNS processes (active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance abuse or substance withdrawal).

68519 ENCEPHALOPATHY, other, specify

68517 EPILEPSY

68685 GAIT OR BALANCE DISORDER

MOTOR DEVELOPMENTAL DELAY

69404

Study participant does not have abnormalities of reflexes, tone or muscle bulk, cognitive development is reasonable but motor landmarks are delayed, for example late walking without weakness, CP, etc.

HIV-ASSOCIATED MYOPATHY

67017 CONFIRMED

1. Symptoms of weakness in proximal muscles (thighs, shoulders, or upper arms) with evidence of proximal weakness on physical examination.

and

2. CPK elevated to greater than twice (>2X) normal (no EMG, physical trauma, or IM injection within 2 weeks).

and

3. ZDV muscle toxicity excluded either by 1) no history of ZDV in the immediately preceding three months or 2) drug holiday from ZDV for at least one month with no improvement in signs, symptoms, or CPK elevation.

and

4. Neurodiagnostic confirmation by either:
    a. EMG documenting myopathic features.

    or

    b. Muscle biopsy documenting myofiber degeneration or inflammation.

67018 PROBABLE

1. Symptoms of weakness in proximal muscles (thighs, shoulders, or upper arms) with evidence of proximal weakness on physical examination.

and

2. CPK elevated to greater than twice (>2X) normal (no EMG, physical trauma, or IM injection within 2 weeks).

and

3. ZDV muscle toxicity excluded either by 1) no history of ZDV in the immediately preceding three months or 2) drug holiday from ZDV for at least one month with no improvement in signs, symptoms or CPK elevation.

67019

Clinical diagnosis only, symptoms of weakness in proximal muscles (thighs, shoulders, or upper arms) with evidence of proximal weakness on physical examination and ZDV muscle toxicity excluded either by 1) no history of ZDV in the immediately preceding three months or 2) drug holiday from ZDV for at least one month with no improvement in signs, symptoms or CPK elevation.

68684 NEUROLOGICAL DEFICIT, FOCAL

68652 NEUROLOGIC SYSTEM DISEASE/DISORDER, other, specify diagnosis

SENSORY PERIPHERAL NEUROPATHY

NOTE: For sensory neuropathy diagnoses that are potentially related to medication, go to the sensory neuropathy diagnosis criteria in the Toxicity Evaluation section of this appendix.

67027 CONFIRMED

1. Symptoms of pain, burning, numbness, or tingling discomfort in both feet, or both feet and hands, for at least 2 weeks. No history of diabetes mellitus, chemotherapy, or vitamin B12 deficiency.

and

2. Examination shows at least two of the following abnormalities:
    a. Diminished or absent ankle reflexes.
    b. Diminished vibration sensation in the toes.
    c. Disturbance in pain or temperature sensation.

and

3. Exclusion of nerve toxicity from ddI, ddC, d4T either by history (no ddI, ddC, or d4T for immediately preceding three months) or by drug holiday off these medications for at least 1 month.

and

4. Neurodiagnostic confirmation by either:
    a. Nerve biopsy.

    or

    b. Abnormal nerve conduction testing *and* abnormal quantitative sensory testing (Vibration CASE IV or equivalent.)

67028 PROBABLE

1. Symptoms of pain, burning, numbness, or tingling discomfort in both feet, or both feet and hands, for at least 2 weeks. No history of diabetes mellitus, chemotherapy, or vitamin B12 deficiency.

and

2. Examination shows at least two of the following abnormalities:
    a. Diminished or absent ankle reflexes.
    b. Diminished vibration sensation in the toes.
    c. Disturbance in pain or temperature sensation.

and

3. Exclusion of nerve toxicity from ddI, ddC, d4T either by history (no ddI, ddC, or d4T for immediately preceding three months) or by drug holiday off these medications for at least 1 month.

67029

Clinical diagnosis only, symptoms of pain, burning, numbness, or tingling discomfort in both feet, or both feet and hands, for at least 2 weeks. No history of diabetes mellitus, chemotherapy, or vitamin B12 deficiency and examination shows at least two of the following abnormalities: diminished or absent ankle reflexes, diminished vibration sensation in the toes and disturbance in pain or temperature sensation.

68516 PERIPHERAL NERVE DISEASE/DISORDER, other, specify diagnosis

68683 SEIZURE DISORDER (NOT EPILEPSY)

XII. OTHER HIV ASSOCIATED DISEASES

RECURRENT APHTHOUS STOMATITIS

64049

Clinical descriptors: Single or multiple, white/yellow, well circumscribed, painful ulcer(s) on non-keratinized tissue. A red halo is usually present around each ulcer. Minor aphthous ulcers may be, 0.2 to 0.5 cm in diameter while major aphthous ulcers are greater than (>) 0.5 cm in size (may be as large as 2 cm in diameter).
Patient reported symptoms: Moderate to severe pain, especially upon eating.
Patient reported duration: Each minor ulcer lasts 7 to 10 days, while major aphthous ulcers may last for weeks. Patient reports a long-term history of recurrent ulcers.

SEBORRHEIC DERMATITIS

This is a clinical diagnosis without definitive criteria.

69027 PROBABLE

1. Itchy, scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin).

UNEXPLAINED PERSISTENT FEVER

69026 CONFIRMED

1. Documented fever of >37.5 º C with negative blood culture, negative Ziehl-Nielsen stain, malaria slide and normal or unchanged chest X-ray and no other obvious foci of infection.

69025 PROBABLE

2. Fever or night sweats for more than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarial agents, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.

NECROTIZING ULCERATIVE GINGIVITIS/ PERIODONTITIS

NOTE: When reporting this diagnosis on a case report form, record as necrotizing ulcerative periodontitis in the specify line.

65014 PROBABLE

Clinical descriptors: Destruction of one or more interdental gingival papillae. In the acute stage of the process ulceration, necrosis, and sloughing may be seen with ready hemorrhage and characteristic fetid odor. In the case of Necrotizing Ulcerative Periodontitis, the condition is characterized by soft tissue loss as a result of ulceration or necrosis. Exposure, destruction or sequestration of alveolar bone may be seen, and the teeth may become loosened.
Patient reported symptoms: Moderate to severe pain may be a prominent feature.
Patient reported duration: Usually of a sudden onset and rapidly worsens.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

64900

1. Initiation, reintroduction or change in antiretroviral therapy/regimen.

and

2. [1] Evidence of:
   a. an increase in CD4+ cell count as defined by ≥50 cells/mm^3 or a ≥2-fold rise in CD4+ cell count, **and/or**
   b. decrease in the HIV-1 viral load of >0.5 log_{10} **and/or**
   c. weight gain or other investigator-defined signs of clinical improvement in response to initiation, reintroduction or change of antiretroviral therapy/regimen.

and

3. Symptoms and/or signs that are consistent with an infectious/inflammatory condition

and

4. These symptoms and/or signs cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of antiretroviral therapy itself.

and

5. For purposes of data collection, the infectious/inflammatory condition must be attributable to a specific pathogen or condition.

[1] If the study participant is being evaluated for an infectious/inflammatory condition at a time that is <4 weeks after initiation, reintroduction or change in antiretroviral therapy/regimen, items 2a-2c are not required.

Refer to the "Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)" section in the ACTG Definition of Immune Reconstitution Inflammatory Syndrome (IRIS) document for specific Opportunistic Infection (OI) and non-pathogen condition diagnosis criteria. The ACTG Definition of Immune Reconstitution Inflammatory Syndrome (IRIS) document is available on the ACTG Network website (www.actgnetwork.org) under Global Protocol Support Documents.

SPECIFIC IRIS CASE DEFINITION for Mycobacterium tuberculosis (TB)

NOTE: All reference numbers listed in brackets for the following section can be found in the ACTG Definition of Immune Reconstitution Inflammatory Syndrome (IRIS) document.

Mycobacterium tuberculosis (TB)
Paradoxical TB-Associated IRIS
64901 CONFIRMED

TB IRIS in patients *with* a prior history of TB (paradoxical TB-associated IRIS):

There are three components to this case-definition [12]:

A) Antecedent requirements

i) Diagnosis of tuberculosis: previous pulmonary (smear positive or smear-negative) or extrapulmonary TB diagnosis by ACTG criteria

AND

ii) Initial response with anti-TB therapy (e.g., stabilization or improvement of signs/symptoms with appropriate anti-TB therapy prior to initiation of ART)*. For example, there has been cessation or improvement of fevers, cough, night sweats.

*Note: This does not apply to patients starting ART within two weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported.

(B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within three months of ART initiation, reinitiation, or regimen change because of HIV treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement, e.g., tuberculous arthritis
- New or worsening radiological features of tuberculosis (found by chest compatible radiography, abdominal ultrasonography, CT, or MRI)
- New or worsening CNS tuberculosis (meningitis or focal neurological deficit; e.g., caused by tuberculoma)
- New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

- New or worsening constitutional symptoms such as fever, night sweats, or weight loss
- New or worsening respiratory symptoms such as cough, dyspnea, or stridor
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded

- Failure of tuberculosis treatment because of tuberculosis drug resistance
- Poor adherence to tuberculosis treatment
- Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative

pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)
- Drug toxicity or reaction

64902 PROBABLE

TB IRIS in patients *with* a prior history of TB (paradoxical TB-associated IRIS):

"Probable" status should be assigned for cases where criteria A and B are met (see confirmed TB IRIS with a prior history of TB definition) but an alternative diagnosis or explanation for clinical deterioration cannot be fully excluded.

Mycobacterium tuberculosis (TB)

ART "UNMASKING" TB-ASSOCIATED IRIS

64911 CONFIRMED

TB IRIS in patients *without* a prior history of TB (ART "unmasking" TB-associated IRIS):

Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfills ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. Active TB develops within three months of starting ART and one of the following criteria is met: heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component. For example, presentations may include TB lymphadenitis or TB abscesses with prominent acute inflammatory features; the development of pulmonary or extrapulmonary TB with no evidence of miliary disease accompanied by marked focal inflammation; or histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, caseation) accompanied by histologic or culture evidence of AFB consistent with TB in the absence of positive cultures for any other AFB.

64912 PROBABLE

TB IRIS in patients *without* a prior diagnosis of TB (ART "unmasking" TB-associated IRIS):

Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfills ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB, or extrapulmonary TB. There is heightened intensity of clinical manifestations but there is not clear evidence of a marked inflammatory component to the presentation or the subsequent development of focal inflammatory site(s) is beyond three months of ART initiation.

HIV-ASSOCIATED NEPHROPATHY

68631

1. Renal biopsy

PROBABLE PNEUMONIA AND/OR ETIOLOGY UNKNOWN
NOTE: This is not to be used for diagnoses of bacterial pneumonia. Refer to the bacterial pneumonia criteria in the Bacterial section of the appendix for the Bacterial Pneumonia diagnoses.

69028

1. Compatible clinical syndrome of pneumonia (e.g., productive cough and fever)

and

2. Radiologic evidence of pulmonary infiltrate.

and

3. No pathogen identified.

WASTING SYNDROME

NOTE: Study participants should be carefully assessed for the concurrent existence of abnormal or altered fat distribution. Diagnostic criteria can be found in the document "Diagnostic Criteria for Abnormalities of Fat Redistribution." This document is located at the ACTG Web Site / Global Protocol Support Documents / Metabolic /Fat Redistribution Guidelines at the following link: http://ACTG.s-3.com/ . You must be a registered user to access the Web Site.

69020 CONFIRMED

EITHER A:

1. Involuntary weight loss of greater than 10% over at least 6 months.

and

2. No evidence of concurrent illness or condition (other than HIV infection) that explains or contributes to the ongoing weight loss (i.e., dehydration, edema, simple mechanical impediments to oral intake).

OR B:

1. Involuntary weight loss of greater than 5% over 3 consecutive months.

and

2. No evidence of concurrent illness or condition (other than HIV infection) that explains or contributes to the ongoing weight loss (i.e., dehydration, edema, simple mechanical impediments to oral intake).

or

3. The weight loss must persist for at least 3 consecutive months despite initiation of appropriate treatment for the known concurrent illness or condition.

PROBABLE

There is no acceptable definition to be used within the ACTG.

69022

Clinical involuntary weight loss >10% of baseline plus chronic diarrhea or chronic weakness and documented fever ≥30 days.

ULCERATIONS NOS (NOT OTHERWISE SPECIFIED)/NECROTIZING ULCERATIVE STOMATITIS, specify ulcerations NOS, oral or necrotizing ulcerative stomatitis when reporting this diagnosis.

65013 CONFIRMED

Histologic features are those of non-specific ulceration. Microbiologic studies fail to identify a specific etiologic agent.

65012 PROBABLE

Clinical descriptors: Large (>0.5 cm and sometimes up to 3 cm) ulceration(s) with white/yellow necrotic base that may be located on either keratinized or non-keratinized mucosa (note: The clinical appearance is similar to that of major aphthous ulcer, but there is no history of recurrent lesions). Necrotizing ulcerative stomatitis presents as localized, painful ulceronecrotic lesions of the oral mucosa that exposes underlying bone or penetrates or extends into contiguous tissues. These lesions may extend from areas of necrotizing periodontitis.
Patient reported symptoms: Severe pain may be a prominent feature.
Patient reported duration: Sudden onset, but may be long-standing and/or recurrent.

OTHER CLINICAL EVENT DIAGNOSIS

69999 CONFIRMED, PROBABLE

HIV associated clinical endpoints or events potentially related to medications not otherwise specified in this appendix. Refer to the CDC Case Definitions of AIDS, the local investigator and/or the protocol team for further guidance.

XIII. CARDIOVASCULAR DISEASES

There is no distinction between confirmed or probable definitions for cardiovascular diseases.

ANGINA PECTORIS

68222

1. History of chest discomfort caused by exertion or excitement and alleviated with rest. May be described as pain but more frequently as heaviness, pressure, squeezing or choking sensation. May radiate to the left shoulder, down the arm, back, neck or jaw.

or

2. Atypical presentation with a report of at least one of the following:
    a. Electrocardiograph consistent with acute ischemia.
    b. Stress test findings consistent with ischemia.
    c. Angiogram of the coronary arteries demonstrating significant occlusion(s), and other etiologies of the presenting signs and symptoms are unlikely.

AORTIC ANEURYSM

68270

Radiographic or surgical evidence of an aortic aneurysm.

68271

Clinical diagnosis only, testing technology not available to determine diagnosis.

ARRHYTHMIA, SIGNIFICANT, specify arrhythmia

68250

A cardiac arrhythmia present on an ECG and/or rhythm strip causing or with the potential to cause clinically significant hemodynamic consequences.

68251

Clinical diagnosis only, testing technology not available to determine diagnosis.

CARDIOMYOPATHY, HIV-ASSOCIATED, SYMPTOMATIC, (WHO Stage 4 guidelines)

68132 CONFIRMED

Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.
Note: It may not be possible to discern the etiology for cardiomyopathy.

PROBABLE

This is a definitive diagnosis without clinical criteria.

DEEP VEIN THROMBOSIS (DVT)

68224 CONFIRMED

1. Clinical presentation of swelling and/or pain/tenderness of one or both lower extremities.

and

2. Findings consistent with DVT on ultrasound, Doppler, computerized tomography (CT) or other acceptable diagnostic method.

68225 PROBABLE

1. Clinical presentation of swelling and/or pain/tenderness of one or both lower extremities.

HYPERTENSION

NOTE: The diagnosis of hypertension should be made by the study participant's clinician and not diagnosed solely on the blood pressure measurements obtained during research visits.

68210

1. A clinical diagnosis of hypertension is based on the average diastolic blood pressure >90 mmHg and/or systolic blood pressure of >140 mmHg in an adult not taking antihypertensive medications and not acutely ill. Based on the average of two or more readings taken at each of two or more visits after the first elevated blood pressure was obtained.

or

2. Antihypertensive treatment or a regimen of diet and exercise prior to starting antihypertensive medication recommended or initiated. This includes initial treatment with diuretics to control the hypertension.

LEFT VENTRICULAR FAILURE

68139

1. One or more of the following: paroxysmal nocturnal dyspnea, or dyspnea at rest, or orthopnea, or New York Heart Classification III.

   (Note: NY Heart Class III* is defined as "Study participant with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain." *1994 Revisions to Classification of Functional Capacity and Objective Assessment of Study participants With Disease of the Heart, AHA.)

and

2. At least one of the following signs must be present: rales, 2+ or greater ankle edema, tachycardia of 120 beats/minute or more after 5 minutes at rest, cardiomegaly by chest X-ray, chest X-ray characteristic of congestive failure, S3 gallop, or jugular venous distention.

68142

Clinical diagnosis only, testing technology not available to determine diagnosis.

LEFT VENTRICULAR HYPERTROPHY

68131

An interpretation of an electrocardiograph indicating findings consistent with diagnosis of left ventricular hypertrophy. (For example, Cornell criteria require the sum of the amplitude of R wave in avL lead and S wave in V3 lead is greater than 28 in males or 20 in females.)

MYOCARDIAL INFARCTION, ACUTE (SYMPTOMATIC)

68220 CONFIRMED

1. Symptoms suggestive of myocardial infarction.

and

2. Cardiology report of electrocardiograph indicating findings consistent with myocardial infarction. (For example, new Q wave present in 2 or more contiguous leads and with either duration ≥ 40 msec or amplitude > ¼ of R wave.)

or

3. Significant elevation of serum enzymes as demonstrated by one of the following:
    a. CPK-MB present, or above upper limit of normal (depending on how local lab records) within 36 hours of onset of acute symptoms of MI.
    b. Reversal of LDH/LDH2 ratio within 5 days of the onset of acute symptoms of MI.
    c. CPK total at least 1.25 times the upper limit of normal for the laboratory that performed the test (in the absence of other possible causes for elevation of the CPK total and with CPK-MB missing, not done, or done more than 36 hours after onset of symptoms).
    d. SGOT, LDH or other cardiac enzymes at least 1.25 times the upper limit of normal for the laboratory that performed the test (in the absence of other possible causes for elevation of the enzymes and with CPK-MB missing, not done, or done more than 36 hours after the onset of symptoms.)
    e. Elevation (> 0.1ng/mL) in serum cardiac-specific troponin I (cTnI) and troponin T (cTnT). (Note: Serum levels of cTnI and cTnT increase 3-12 hours after onset of MI, reach a peak in 24-48 hours, and return to baseline over 5-14 days.)

68221 PROBABLE

Clinical diagnosis only, testing technology not available to determine diagnosis.

MYOCARDIAL INFARCTION, SILENT (found at routine ECG or on hospital ECGs**)**

68223

Cardiology report of electrocardiograph indicating findings consistent with myocardial infarction. (For example, new Q wave present in two (2) or more contiguous leads and with either duration ≥ 40 msec or amplitude > ¼ R wave.)

PERIPHERAL VASCULAR DISEASE (PVD)

NOTE: Intermittent claudication is a symptom of peripheral vascular disease. Report only diagnoses of PVD using this diagnosis code. Symptoms in the absence of a physician's diagnosis should be reported on a sign and symptom form.

68141

1. Recurring episodes of pain, ache, cramp, numbness or sense of fatigue in either leg (usually calf) occurring during exercise. (intermittent claudication)

and

2. Symptom(s) does not resolve during exercise but is relieved with rest.

PULMONARY EMBOLUS

68160 CONFIRMED

Radiographic evidence of an embolus in the pulmonary tree.

68161 PROBABLE

Signs and symptoms consistent with a thrombosis in the pulmonary tree, radiographic evidence non-diagnostic or not done.

STROKE, specify hemorrhagic, ischemic, or unknown

68180

1. Demonstrable lesion compatible with an acute stroke on a CT (or MRI).

or

2. Rapid onset of a neurologic deficit persisting for at least 24 hours which is:
    a. Attributed to an obstruction or rupture of the arterial system.

    and

    b. Not known to be secondary to brain trauma, tumor, infection or other cause.

For study participants that satisfy the above criteria, select the type of stroke:

A. HEMORRHAGIC STROKE

1. Blood in subarachnoid space or intraparenchymal hemorrhage by CT scan. (Intraparenchymal blood must be dense and not mottled-mixed hyperdensity and hypodensity.)

or

2. Bloody spinal fluid by lumbar puncture. (Bloody CSF means >100 cells/cu mm. The LP is thought to be non-traumatic and counts in the last tube are similar to those in the first tube [no clearing] or xanthochromia when the specimen is spun down.)

or

3. Surgical evidence of hemorrhage as cause of clinical syndrome.

B. ISCHEMIC INFARCTION

1. Focal brain deficit without CT or LP evidence of blood, except mottled cerebral pattern. Either decreased density by CT in a compatible location or a negative CT or none done.

or

2. Surgical evidence of ischemic infarction.

C. UNKNOWN TYPE OF STROKE

Inadequate information to categorize as hemorrhagic or ischemic infarction. Satisfies criteria for stroke.

68181

Clinical diagnosis only, testing technology not available to determine diagnosis.

TRANSIENT ISCHEMIC ATTACK

NOTE: Discovery of an infarct by CT in a location compatible with the symptoms, even if the symptoms cleared in less than 24 hours, shall be diagnosed as a stroke.

68183

1. One or more episodes of focal neurologic deficit lasting more than 30 seconds and no longer than 24 hours with rapid evolution of the symptoms to the maximal deficit in less than 5 minutes with complete resolution and no immediately preceding head trauma.

and

2. There should be no evidence of clonic jerking, conjugate eye deviation, prolonged Jacksonian march, scintillating scotoma, headache with nausea and vomiting.

OTHER CARDIOVASCULAR DISEASES

68132 CARDIOMYOPATHY, HIV-related

68143 CARDIOMYOPATHY, drug-induced

68144 CARDIOMYOPATHY, etiology unknown

68145 PULMONARY HYPERTENSION

68146 SHOCK

68148 HYPOTENSION

68199 CARDIOVASCULAR SYSTEM DISEASE/DISORDER, other, specify

XIV. TOXICITY EVALUATION

The following diagnoses may or may not be related to medications that the study participant is receiving

---

CORONARY HEART DISEASE (CHD)/ CORONARY ARTERY DISEASE (CAD)
See ALSO Appendix Section XIII-Cardiovascular Diseases for specific cardiovascular diagnoses

68147

The Cardiovascular Diseases Study Group recommends that we use the term CHD (coronary heart disease) in order to include all clinically suspected and/or angiographically confirmed CAD (coronary artery disease).

Disease State Description

None

DIABETES MELLITUS/IMPAIRED GLUCOSE

68021 IMPAIRED FASTING GLUCOSE
68022 IMPAIRED GLUCOSE TOLERANCE
68023 DIABETES MELLITUS

Normoglycemia:	Fasting plasma glucose of <110 mg/dL *or* 2-hour post glucose load plasma glucose <140 mg/dL.
Impaired Fasting Glucose:	Fasting plasma glucose of ≥110 mg/dL and <126 mg/dL.
Impaired Glucose Tolerance:	2-hour post glucose load plasma glucose ≥140 mg/dL and <200 mg/dL.
Diabetes Mellitus:	Fasting plasma glucose ≥126 mg/dL *or* 2-hour post glucose load plasma glucose ≥200 mg/dL *or* non-fasting plasma glucose ≥200 mg/dL accompanied by symptoms of diabetes mellitus (polyuria, polydipsia, dehydration, blurred vision, new vaginal candidiasis).

NOTE: If an ACTG study participant has a fasting plasma glucose value suggestive of a diagnosis of diabetes but no other symptoms of diabetes, the fasting glucose value must be confirmed.

Disease State Description:

Level A: Impaired fasting glucose
Level B: Impaired glucose tolerance
Level C: Diabetes Mellitus

FAT ACCUMULATION (LIPODYSTROPHY)

67221

Symptoms due to fat accumulation in various places occur following the initiation or change of antiretroviral therapy. These include increasing abdominal girth with an increasing belt or waist size which may be accompanied by complaints of bloating or distension; fat accumulation in the back of the neck or increasing neck size; increasing breast size which may be accompanied by complaints of breast pain; and other new fat accumulations either circumscribed (lipomas) or general such as increase in chest size in absence of breast enlargement. In reporting fat accumulation, the body area involved needs to be specified. In males gynecomastia can present as unilateral breast enlargement, occasionally with nodular lesions.

Abdominal and/or Truncal Obesity:

Possible: Self-report of increasing abdominal girth; increasing belt or waist size (may be accompanied by complaints of bloating, distension)

Definite:

- Cross-sectional: Self-reported increase plus waist-to-hip ratio (WHR) > 0.95 (M); 0.85(F)
- Longitudinal: Measured increase in waist circumference of 2.5 cm (1") or 5% increase in WHR, sagittal diameter, or abdominal fat (by paired MRI, DEXA, or CT measurements obtained under identical, controlled conditions) in the past 12 months

Dorsocervical Fat Pad Enlargement (Buffalo Hump):

Possible: Self-report of increasing size of dorsocervical region; may be accompanied by increasing shirt neck size or inability to button shirts

Definite:

- Cross-sectional: Physical findings consistent with accumulations of fat in dorsocervical area
- Longitudinal: Measured increase in neck circumference of 1.5 cm (0.5") in the past 12 months

Breast Enlargement (Both Genders):

Possible: Self-report of increasing bra size or shirt/blouse size to accommodate increasing breast size; may be accompanied by complaints of breast pain

Definite:

- Cross-sectional: Self-reported increase plus physical findings consistent with enlarged breasts due to increase in fat deposition (note: gynecomastia is an increase in breast tissue, a distinct syndrome and finding)
- Longitudinal: Measured increase in chest circumference of 5% in past 12 months

Other New Fat Accumulation (Must Specify Location):

Possible: Self-report of new regional circumscribed accumulation of fat; increase in neck size in absence of dorsocervical fat pad enlargement; increase in chest size in absence of breast enlargement.

Definite:

- Cross-sectional: Self-report of new fat accumulation plus physical findings consistent with lipoma(s) or lipomatosis (multiple fat accumulations or one > 2 cm)

Disease State Description:

Level A: Study participant and/or only close friends/family notice the changes.

Level B: Physical evidence of fat accumulation noted by physician and confirmed by study participant.

Level C: Increase in regional fat is very concerning to the study participant and very obvious to others.

FAT LOSS (LIPOATROPHY)

67215

Face — Study participant may report "sunken cheeks" or "drawn face" or indicate that family members or friends have noticed such changes since initiation or change of antiretroviral therapy. The loss of facial tissue should be just proximal to the nasolabial fold. (This is the area of the buccal fat pad, the largest fat deposit in the face.)

Extremities — Study participant reports that pants/slacks are progressively fitting more loosely through the thighs, new onset of looseness of watch or wristbands, and awareness that the extremities appear thinner since the initiation or change of antiretroviral therapy. The relationship is strengthened by reporting of awareness that veins in the extremities appear more prominent. On exam, extremities appear thin and veins prominent.

Buttocks — Self-reported change in the buttocks in which there is a perception of loss of volume in the subgluteal region, since the initiation or change of antiretroviral therapy. Loss of firmness is by itself not diagnostic as it could be due to muscle atrophy.

Disease State Description:

Level A: Study participant and/or only close friends/family notice the changes
Level B: Physical evidence of fat depletion noted by physician and confirmed by study participant
Level C: Loss of fat is very concerning to the study participant and very obvious to others, or 25% decrease in fat as documented by paired measurement of BIA, DEXA, ultrasound (for facial LA) or MRI.

LACTIC ACIDEMIA/ LACTIC ACIDOSIS

68657 HYPERLACTACIDEMIA (LACTIC ACIDEMIA), specify Asymptomatic or Symptomatic

68654 LACTIC ACIDOSIS

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 "ACTG Venous Lactate Specimen Collection and Storage Guidelines" at http://ACTG.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 < 2x upper limit of normal (ULN) confirmed by repeat lactate level analysis

Level B: Asymptomatic lactic acidemia ≥ 2x upper limit of normal (ULN) confirmed by repeat lactate level analysis

Level C: Symptomatic lactic acidemia or lactic acidosis.

LIVER DISEASE, specify type (this includes but is not limited to the most common causes listed below)
If there is a diagnosis of Chronic Hepatitis B or Chronic Hepatitis C, refer to Appendix Section IV-Viral Infections, for criteria.

68511

Development of abnormal liver enzymes (ALT and/or AST and/or alkaline phosphatase) or elevation in bilirubin in a study participant with previously normal tests, or further increases (to grade ≥ 3) in a study participant with chronic abnormal levels. Most common causes in HIV-infected study participants are drug injury, viral hepatitis, steatosis, cholelithiasis, tumors, and other non-drug related conditions. In study participants with known chronic hepatitis B or C, certain drugs may worsen already present liver abnormalities, e.g., nevirapine (hepatocellular damage), indinavir and atazanavir (unconjugated bilirubinemia), lopinavir/ritonavir (hepatocellular damage), etc.

1. In study participants with normal liver tests prior to initiating or changing antiretroviral therapy, the following evaluations are recommended.

    a. History, physical examination, blood count, liver chemistries, ultrasound of the liver, liver biopsy (optional) and laboratory tests for viral hepatitis:
        i. HAVAb IgM (for acute disease; test HAVAb IgG if negative; vaccinate if HAVAb IgG negative)
        ii. HbsAg, HbcAb total (HBV DNA if either is positive)
        iii. HCVAb (HCV RNA if positive or CD4 <200)

2. In study participants with abnormal liver tests prior to initiating or changing antiretroviral therapy, assessment of the cause should be undertaken:
    a. As in previous section
    b. If chronic HBV, test HBV DNA
    c. If chronic HCV, test HCV RNA
    d. Liver biopsy strongly recommended to assess amount of inflammation and stage of fibrosis

3. All study participants with suspected drug-related liver disease must have:
    - No evidence of acute viral hepatitis
    - No evidence of tumor
    - No evidence of cholelithiasis
    - No evidence of non-drug related hepatic injury

Disease State Description

Level A: Elevation in hepatic transaminase and/or bilirubin only.
Level B: Elevation in hepatic transaminase and/or bilirubin plus clinical symptoms suggestive of liver disease.
Level C: Hospitalization, severe liver disease, or death due to liver disease.

68632 NEPHROPATHY, DRUG-INDUCED

HIV-ASSOCIATED NEUROMUSCULAR WEAKNESS SYNDROME

68007

New onset of limb weakness in an HIV-infected individual, with or without sensory involvement; either acute (7-14 days) or subacute (>14 days) and affecting either lower or both lower and upper extremities.

NOTE: Abnormal lactic acid is not required for the definition.

Probability diagnosis based on:

Possible: Consistent clinical features
Probable: Confounding diagnosis excluded with work-up
Definite: NCV/EMG and/or nerve/muscle biopsy confirmation of neuromuscular disease

Disease State Description:

Level A: Muscle weakness appreciable, but not significantly limiting everyday functioning.
Level B: Muscle weakness significantly limiting everyday functioning (e.g., walking, climbing stairs, carrying groceries).
Level C: Muscle weakness resulting in requiring a wheelchair, being bed bound, or requiring respiratory support.

SENSORY NEUROPATHY

68009

1. New or recurrent sensory symptoms bilaterally in the lower extremities for at least 14 consecutive days, including numbness or parasthesias (tingling) or dysesthesias (burning, shooting or stabbing pain), spontaneous or evoked.

and

2. Reduced or absent ankle reflexes

and

3. Abnormal sensory exam: reduced pinprick or reduced vibration.

Disease State Description:

Level A: Meets the case definitions. No therapy required.
Level B: Symptomatic therapy required. No limitation of ADLs.
Level C: Therapy required and ADLs are limited by the neuropathy.

Note: ADLs are activities of daily living such as ambulation, bathing, dressing, grooming, feeding, toileting.

OSTEOPENIA/OSTEOPOROSIS

68674 OSTEOPENIA
68675 OSTEOPOROSIS

Osteopenia/osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. The only difference between the terms is the grade, osteopenia being less severe as determined by dual-energy X-ray absorptiometry (DEXA) t-score.

Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70 percent of bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 standard deviations below the mean for young white adult women. It is not clear how to apply this diagnostic criterion to men, children, and across ethnic groups. *By extension these criteria are used in those groups (comparing to individuals of the same gender and race at age 30 in adults, and same-age children).*

Several different techniques have been developed to assess BMD at multiple skeletal sites including the peripheral skeleton, hip and spine. The World Health Organization (WHO) has selected BMD measurements to establish criteria for the diagnosis of osteoporosis. Although t-scores were based originally on assessment of BMD at the hip by DEXA, they have been applied to define diagnostic thresholds at other skeletal sites and for other technologies.

World Health Organization (WHO) criteria for diagnosis of osteoporosis based on BMD:

Normal t-score ≥ -1
Osteopenia t-score > -2.5 but < -1
Osteoporosis t-score ≤ -2.5
Severe Osteoporosis t-score ≤ -2.5 *and* evidence of fragility fracture

NOTE: If an ACTG study participant has clinical evidence of osteoporosis but has not received a DEXA scan, the primary care provider should obtain a DEXA scan to quantify the study participant's BMD.

Disease Sate Description

Level A: Osteopenia (t-score < -1 but > -2.5)
Level B: Osteoporosis (t-score ≤ -2.5)
Level C: Severe osteoporosis (t-score ≤ -2.5 and evidence of fragility fracture)

PANCREATITIS DOCUMENTATION

68625 CLINICAL OR SYMPTOMATIC

Clinical or symptomatic pancreatitis is defined by the symptoms of nausea, vomiting, and/or abdominal pain of any duration associated with ≥ Grade 3 elevations of lipase (>2.0 x ULN) and without other non-pancreatic diagnoses to reasonably account for the presentation. Symptoms associated with persistent elevations of lipase < Grade 3 require radiographic evaluation, preferably by CT scan, to confirm the diagnosis. If radiographic evaluation does not confirm pancreatitis, symptoms and lipase evaluated every two weeks until resolution or progression to confirmed pancreatitis. The severity level of pancreatitis is determined by the highest severity of the symptoms.

68626 CHEMICAL *OR* ASYMPTOMATIC

Chemical or asymptomatic pancreatitis is defined as persistent (2 determinations, 2 weeks apart) elevations in lipase ≥ Grade 3. Severity for chemical pancreatitis in absence of symptoms is always rated as mild.

68628

Clinical diagnosis only, testing technology not available to determine diagnosis. Clinical symptoms < Grade 3 and no radiographic evaluation available.

DRUG-RELATED RASH (not hypersensitivity reaction)

This is a clinical diagnosis without definitive criteria.

68529 PROBABLE

Papular pruritic lesions, often with marked post-inflammatory pigmentation.

RENAL INSUFFICIENCY, ACUTE

68025

Increases in serum creatinine to values >1.5 mg/dL (or >1.0-1.3 x ULN) that return to normal values within 3 months or less.

Disease State Description

Score yes/no.

RENAL INSUFFICIENCY, CHRONIC

68026

Increases in serum creatinine to values >1.5 mg/dL (or >1.0-1.3 x ULN) that persist for > 3 months.

Disease State Description

Level A: Medication dosage adjustments not required.
Level B: Medication dosage adjustments required.
Level C: Requires dialysis.

NEUROPSYCHIATRIC CONDITIONS TOXICITY EVALUATION

68345 ANXIETY

Anxiety is defined as a new onset of persistent and excessive anxiety and worry for at least 10 out of 14 consecutive days.

Disease State Description:

Level A: Meets case definition.
Level B: Symptoms require treatment or interfere with usual activities or 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.

68682 DEPRESSION

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)

NOTE: If symptoms listed above are used to make the diagnosis of depression, do not fill out separate Tox-EG forms for individual neuropsychiatric conditions.

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.

68043 DREAM ABNORMALITY

Dream abnormality is defined as new onset of abnormal dreams which are described by the study participant as vivid, bizarre or frightening and which have been present for at least 4 days out of 7 consecutive days.

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 dream 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.

68042 DROWSINESS

Drowsiness is defined as new or worsening pathologic increase in absolute sleep hours by 25%, present for at least 7 of 14 consecutive days.

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 drowsiness *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.

68038 HALLUCINATIONS

Hallucinations is defined as new onset and presence of false visual, auditory, tactile, olfactory or gustatory perceptions that have no basis in external stimulation.

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 hallucinations *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.

68035 HYPOMANIA/MANIA

1. A hypomanic episode is defined as a distinct period of abnormal and persistently elevated, expansive mood lasting at least 3 out of 4 consecutive days. A manic episode is defined as a distinct period of abnormal and persistently elevated, expansive mood lasting at least 6 out of 7 consecutive days.

and

2. Three or more of the following: Inflated self-esteem, decreased need for sleep (feels rested after only 3 hours of sleep), pressure to keep talking, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity, excessive and risky pleasure-seeking (e.g., unrestrained buying sprees, sexual indiscretions, foolish investments, etc.).

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.

68041 INSOMNIA

Insomnia is defined as new or worsening insomnia at least 7 days out of 14 consecutive days and characterized by difficulty in falling asleep or in staying asleep or by disturbed sleep patterns resulting in insufficient sleep.

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 insomnia *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.

68036 PSYCHOSIS

Psychosis is defined as a new onset and presence for at least 2 days out of 14 consecutive days of delusional thought patterns (e.g., thoughts of persecution, thought broadcasting, thought insertion, or thoughts of reference) or disorganized speech or grossly disorganized or catatonic behavior.

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 psychosis *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.

68037 SUICIDAL IDEATION

Suicidal Ideation is defined as new onset of suicidal thoughts.

Disease State Description:

Level A: Suicidal thoughts only.
Level B: Study participant has suicidal thoughts *and* a suicide plan.
Level C: Study participant has attempted suicide.

XV. OTHER DISEASE CODES

These codes are to be used to report diagnoses not specified in other sections of this appendix.

DERMATOLOGIC

68521 SKIN DISEASE/DISORDER, OTHER, specify diagnosis

68525 STEVENS-JOHNSON SYNDROME

68524 STUDY DRUG RELATED HYPERSENSITIVITY REACTION

68601 OTHER DRUG-INDUCED HYPERSENSITIVITY REACTION (i.e. Abacavir-like)

GASTROINTESTINAL

68510 GASTROINTESTINAL SYSTEM DISEASE/DISORDER, OTHER, specify diagnosis

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GENITOURINARY

68526 NEPHROLITHIASIS

68527 PROXIMAL RENAL TUBE DYSFUNCTION (PRTD) (Fanconi-like syndrome)

68512 RENAL SYSTEM DISEASE/DISORDER, OTHER, specify diagnosis

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METABOLIC/ENDOCRINE

68650 DIABETIC KETOACIDOSIS

68653 HYPOGONADISM

68655 LIPID ABNORMALITY, specify abnormality

68656 WEIGHT LOSS (See Appendix Section XII - Other HIV Associated Diseases for Wasting Syndrome)

MUSCULOSKELETAL

68670 ARTHRITIS, specify type

68671 AVASCULAR NECROSIS

68672 FRACTURE

68528 MYOSITIS

68518 MUSCULOSKELETAL SYSTEM DISEASE/DISORDER, OTHER, specify diagnosis

NEUROLOGIC AND/OR PSYCHIATRIC

68680 ALCOHOL ABUSE

68681 SUBSTANCE ABUSE, specify

68686 MENTAL STATUS IMPAIRMENT

68687 MOOD DISORDERS

68515 PSYCHIATRIC DISEASE/DISORDER, OTHER, specify diagnosis

PULMONARY

68690 ASTHMA

68691 PNEUMOTHORAX

68692 RESPIRATORY FAILURE

68507 RESPIRATORY DISEASE/DISORDER, OTHER, specify diagnosis

STD

69611 CHANCROID, specify site

69605 CHLAMYDIA TRACHOMATIS

69604 NEISSERIA GONORRHEA

69610 SYPHILITIC ULCER, specify site

68700 SYPHILIS

69603 TRICHOMONAS VAGINALIS

69612 WARTS (EXCLUDING ORAL), specify site

68522 VENEREAL DISEASE, OTHER, specify diagnosis

OTHER GENERAL DIAGNOSES CODES

68501 ALLERGY, specify diagnosis

68502 EYE, EAR, NOSE DISEASE, specify diagnosis

68520 HEMATOLOGIC DISEASE (other than clotting disorder), specify diagnosis

68523 HEMOPHILIA

68503 MOUTH OR THROAT DISEASE, specify diagnosis

68513 REPRODUCTIVE SYSTEM DISEASE/DISORDER, MALE OR FEMALE, specify diagnosis

68599 OTHER EVENT NOT LISTED IN APPENDIX 60, non HIV-associated

DIAGNOSES INDEX

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