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# The Use of the Medical Dictionary for Regulatory Activities in the Identification of Mitochondrial Dysfunction in HIV-Infected Children

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***Objective.*** *To demonstrate the utility of a medical terminology-based method for identifying cases of possible mitochondrial dysfunction (MD) in a large cohort of youths with perinatal HIV infection and to describe the scoring algorithms.*
***Methods.*** *Medical Dictionary for Regulatory Activities (MedDRA)® version 6 terminology was used to query clinical criteria for mitochondrial dysfunction by two published classifications, the Enquête Périnatale Française (EPF) and the Mitochondrial Disease Classification (MDC). Data from 2,931 participants with perinatal HIV infection on PACTG 219/219C were analyzed. Data were qualified for severity and persistence, after which clinical reviews of MedDRA-coded and other study data were performed.*
***Results.*** *Of 14,000 data records captured by the EPF MedDRA query, there were 3,331 singular events. Of 18,000 captured by the MDC query, there were 3,841 events. Ten clinicians blindly reviewed non MedDRA-coded supporting data for 15 separate clinical conditions. We used the Statistical Analysis System (SAS) language to code scoring algorithms. 768 participants (26%) met the EPF case definition of possible MD; 694 (24%) met the MDC case definition, and 480 (16%) met both definitions.*
***Limitations.*** *Subjective application of codes could have affected our results. MedDRA terminology does not include indicators of severity or persistence. Version 6.0 of MedDRA did not include Standard MedDRA Queries, which would have reduced the time needed to map MedDRA terms to EPF and MDC criteria.*
***Conclusion.*** *Together with a computer-coded scoring algorithm, MedDRA terminology enabled identification of potential MD based on clinical data from almost 3000 children with substantially less effort than a case by case review. The article is accessible to readers with a background in statistical hypothesis testing. An exposure to public health issues is useful but not strictly necessary.*

Abbreviations: *MedDRA, Medical Dictionary for Regulatory Activities; PACTG, Pediatric AIDS Clinical Trials Group; EPF, Enquête Périnatale Française; MDC, Mitochondrial Disease Classification; HIV, Human Immunodeficiency Virus; LLT, Lowest Level Term; HLGT, High Level Group Term; HLT, High Level Term; PT, Preferred Term; SOC, System Organ Class; NIAID, National Institute of Allergy and Infectious Disease; DAIDS, Division of Acquired Immunodeficiency Syndrome; MSSO, MedDRA Maintenance and Support Services Organization, SMQ; Standard MedDRA Query*

## 1. Introduction

Identifying complex medical conditions utilizing large clinical databases is a challenging process, which requires manual or computational data retrieval and clinical classification that is specific enough to allow reasonable case identification (Brophy et al., 2006; Lin et al., 2006; Webster et al., 2006). We analyzed data from a prospective, observational study of almost 3000 children with pediatric HIV disease, followed from birth to 24 years of age, to understand whether there was an association between clinically defined mitochondrial dysfunction (MD, an illness due to a malfunction of the mitochondria, the sections of a cell that generate energy for it) and exposure to selected antiretroviral medications, one of several proposed etiologies (causes) for MD (Crain et al., 2010). When clinical symptoms, diagnoses, and laboratory abnormalities suggest MD, definitive diagnosis of MD requires tissue for histopathology, enzymology, respiratory chain function, and molecular genetics testing, (Andreu and DiMauro, 2003; Bernier et al., 2002; DiMauro, 1998; DiMauro, 2004; DiMauro and Schon, 2003; Scaglia, 2004; Wolf and Smeitink, 2002; Walker et al., 2002), data which were not available from the parent study. In their absence, we applied two published criteria for clinical signs and symptoms associated with MD: the Enquête Périnatale Française (French Pediatric Cohort, EPF; Appendix 1 (Barret et al., 2003; Blanche et al., 1999; Brogly et al., 2007) and the Mitochondrial Disease Classification (MDC; Appendix 2) (Wolf and Smeitink, 2002).

Our objective in this paper is to demonstrate how we processed a complex set of data using a medical terminology system, in particular, the Medical Dictionary for Regulatory Activities (MedDRA)® (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009; Maintenance and Support Services Organization, 2012; Maintenance and Support Services Organization, 2009) to filter large amounts of disparate data, enabling further clinical review and statistical analysis. We also summarize the scoring algorithms which we used to identify cases of possible mitochondrial dysfunction and compare the two sets of findings. SAS code and de-identified data are provided.

### *Background*

The EPF algorithm targets 24 clinical conditions and classifies them as either major or minor criteria affecting neurologic or other organ systems (Appendix 1). MD "cases" are defined by the occurrence of at least one major condition on a single occasion or at least two minor conditions on each of two occasions, not necessarily at the same time (Barret et al., 2003; Blanche et al., 1999; Brogly et al., 2007). In contrast, the MDC algorithm classifies 40 clinical conditions into three presenting organ systems (muscular, central nervous system, and multi-system) (Appendix 2). Points are accrued for each condition reported, up to a maximum of four points according to the presenting system. Metabolic and morphological criteria can each provide up to four additional points, for a maximum of twelve points (Wolf and Smeitink, 2002). With primarily clinical data, a maximum score of four points is possible.

The MedDRA terminology is a large and detailed set of terms that provides internationally recognized categories for each coded event (Maintenance and Support Services Organization, 2012; Maintenance and Support Services Organization, 2009; Brown, 2004). MedDRA is a multi-axial system, which allows for classification of a particular Preferred Term (PT) into more than one System Organ Class (SOC), High Level Group Terms (HLGT) and High Level Terms (HLT). Coding is done from the Lowest Level Term (LLT) level upward through the hierarchy. LLTs correspond to what might be written on a study case report form and are grouped into PTs, each representing a unique clinical or laboratory event. Each LLT maps to one and only one PT; however multiple LLTs may map to the same PT. The MedDRA terminology also includes terms for medical procedures and medical device functioning, and for social and environmental circumstances. Examples of SOCs include: Blood and lymphatic system disorders; Cardiac disorders, Eye disorders; Congenital, familial and genetic disorders. Coding conventions determine which SOC will be primary.

For a previous study utilizing the same parent database as ours, researchers performed case by case reviews to identify mitochondrial dysfunction in young children perinatally exposed to HIV but without HIV infection (Brogly et al., 2007). Although our study drew on children from the same parent study, we examined those children with perinatal HIV infection. As a result, there were many more participants and many more clinical events and resulting data entries to review. A case-by-case review would have been prohibitive. Here, we will show how we used MedDRA terminology to prepare for further analysis.

## 2. Methods

The study population was derived from the Pediatric AIDS Clinical Trials Group (PACTG) protocols 219 and

219C: Pediatric Late Outcomes Protocol, which prospectively followed participants for long-term outcomes of HIV treatment with the goal of assessing late outcomes and complications of HIV infection and exposure to antiviral medications used to treat this infection (Brogly, et al., 2005; Gona, et al., 2006; Ylitalo, et al., 2006; Nachman, et al., 2009). PACTG 219 opened in 1993; participants were children of HIV-infected women enrolled in perinatal treatment trials and children with HIV enrolled in PACTG HIV treatment clinical trials. A later version (219C) was opened in 2000 to all children with HIV within the PACTG and to children and youth from birth to 24 years of age with maternal HIV infection as their primary risk factor. Study sites obtained approval from their respective Institutional Review Boards for Human Research and written consent from the child's parent or guardian. The study closed in May 2007 after enrolling 5,845 children (3,531 HIV infected, 2,238 uninfected, and 76 with unknown status). We restricted our study to participants with confirmed perinatal HIV infection who had been on study for at least six months and who had at least two laboratory visits at the time of their last study visit or by May 3, 2005, the date at which our dataset was retrieved for analysis (n=2931).

HIV-infected children and adolescents were followed with clinical exams and laboratory studies at three month intervals. Physical findings, clinical diagnoses, and diagnostic laboratory test results (HIV-related virology, immunology, hematology and chemistry) were recorded at each visit according to the protocol schedule, while neuropsychological testing occurred less frequently. More specialized examinations (e.g., echocardiography and audiometric testing) were performed as clinically required. Data from case report forms were already being coded using MedDRA for the purpose of safety reporting. Where events were graded according to the DAIDS toxicity tables, in most cases, we applied broad definitions of abnormality and included those events that reflected the need for more than minimal clinical intervention, e.g., moderate (grade 2) or more severe.

## 2.1. MedDRA coding and case definition mapping

Data designated for MedDRA coding in 219/219C included diagnoses, signs and symptoms, and laboratory investigations. Events were graded by clinical sites using the National Institute of Allergy and Infectious Diseases (NIAID) Division of Acquired Immunodeficiency Syndrome (DAIDS) 1994 Toxicity Tables. Reported events were then coded by experienced and qualified MedDRA coders for the purpose of safety reporting and stored in a central database known as the 'events table'. This provided us with a large database to use for our study. Diagnosis events from hospitalization case report form data, which were separately MedDRA-coded, were added to the study database. Each event was assigned a Lowest Level Term (LLT), which in turn was automatically categorized into the MedDRA five-level hierarchy (Figure 1 shows an example of the clinical event Dysphemia (stuttering), in which case the LLT and PT are identical and only the PT term is shown). Quality assurance of the MedDRA code assignment was ongoing throughout the study collection, ensuring consistency in code assignment for similar events. Quality assurance review took into account changes in coding conventions during the study collection period. The MedDRA version remained static during the collection period, with all data records coded in MedDRA version 6.0.

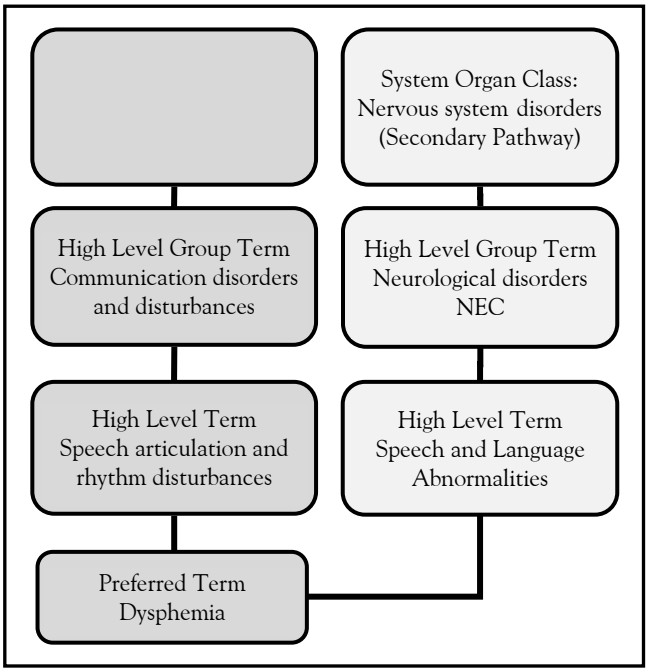


**Figure 1.** MedDRA Hierarchy for PT Dysphemia.

To build the case definition mapping, all MedDRA High Level Group Terms (HLGT) and High Level Terms (HLT) were searched manually for terms meeting clinical criteria specified by the two case definitions used in this study. HLGTs and HLTs of interest were then further expanded to the Preferred Term (PT) level. Lowest Level Terms (LLT) were also examined in some cases, as colloquial terms and/or synonyms are only represented at this level, and in some instances this specificity was needed. Only primary pathways were used when searching the MedDRA hierarchy. Each of the 24 diagnostic criteria for the EPF and 41 for the MDC case definitions was represented by one or more MedDRA sub-queries, each comprised of varying numbers of PT terms. The selected MedDRA terms associated with each

set of diagnostic criteria were reviewed by clinicians to ensure accurate assignment. Any term referring to a condition where an etiology other than potential mitochondrial disease was specifically stated or implied was eliminated; e.g., conditions resulting from trauma. Database records matching the final group of selected MedDRA terms constituted the results of our MedDRA query. Each set of terms for a diagnostic-specific condition constituted a "sub-query". Summary statistics included the number of unique PTs that defined each condition-specific sub-query, the number of unique PT terms captured in our database, and the number of "hits," that is, the number of instances of each PT term within each sub-query, counting at most one per participant.

We also reviewed study data that were not MedDRA coded (e.g., echo-cardiograms, growth data, birth characteristics, ungraded laboratory values such as albumin and neuropsychological test results) to identify objective events that may not have been reported as diagnoses and therefore would not have been coded in the events dataset. These supplemental data also were used to rule out explanatory conditions other than MD.

## 2.2. Case Assignment

There were several stages in the process of applying the EPF and MDC case definitions to our MedDRA coded data. First, we grouped the results of the original MedDRA query into clinical conditions relevant to our scoring algorithms. Graded events were only included in this study if they were abnormal (grade 2 or more severe). All laboratory events were required to be abnormal on at least two sequential visits (persistence required a minimum of three months duration). Other conditions required ascertaining the age at onset, whether or not more than one event occurred, or whether an event occurred multiple times. For example, in the EPF classification, major febrile seizures must have occurred by 6 months of age or there must have been 2 or more episodes.

We also developed relevant clinical definitions for diagnoses associated with laboratory or neuropsychological test abnormalities. For example, we used a combination of CPK (Creatine PhosphoKinase) laboratory test results and myalgia symptoms to identify rhabdomyolysis (MDC). For reduced muscle power (EPF), in the absence of a diagnosis, we used the result of testing with the Bayley Scales of Infant Development (Bayley, 1969; Bayley, 1993) reflecting impaired motor function in the presence of normal neurocognitve function.

### Clinical Validation

Wherever possible we verified clinical diagnoses by laboratory or physical findings, through a mixture of computer-based algorithms and/or clinician reviews. Clinicians reviewed echocardiogram results for cardiomyopathy diagnoses; for sensorineural hearing loss, audiometric exam data were reviewed. Growth measures were subject to both computer and clinical reviews. For acquired microcephaly, head circumference data were used to identify participants with initially normal measurements but who had subsequent poor head growth, and we constructed a new "PT term" (Low Head Circumference) to document these cases. Similarly, for short stature, we identified whether height was below the 3rd percentile or more than 2 standard deviations below the age- and sex-normed mean on at least two sequential visits and called the constructed PT term "Low height measures". Other constructed PT terms were based on low body weight (grouped under "failure to thrive") and on significant, moderate or mildly impaired Weschler and Bayley neurodevelopmental test scores (delayed psychological development conditions). Clinicians also reviewed potential cases and filtered out unconfirmed events. In each clinician review, blinding was maintained with regard to a child's other conditions.

#### *Scoring Algorithms*

We then applied the published scoring algorithms for the EPF and MDC criteria to our MedDRA-coded data and determined whether or not each participant met case criteria, and the date at which the event occurred (e.g., the highest MDC score, or the earliest date at which the EPF criteria were satisfied, along with other summary variables such as the date of each incremental MDC point). We coded the scoring algorithms using the Statistical Analysis System (SAS) v9 (SAS Institute Inc., 2002-2003) We have provided the SAS input datasets and scoring code for each algorithm as well as the code used to generate the comparison between EPF and MDC results (refer to Appendix 3 for the list of programs and datasets provided). All data have been de-identified and patient identifiers have been randomly assigned to protect the confidentiality of the research participants. Dates are represented as days since birth. Cohen's kappa coefficient was used to assess agreement between scoring methods and McNemar's test of asymmetry was used to assess whether more cases were identified by either published algorithm (Agresti, 1996).

For each algorithm, we assigned a numerical code to represent specific clinical conditions, corresponding to those listed in Appendix 2 or their components. Refer to

the SAS format codes, "q1f" (EPF) and "q2f" for the value lists (MDC; Appendix 3, Program mito_tmpformat_meth.sas). The EPF algorithm required that either one of the 16 major clinical conditions or two of the eight minor conditions (each occurring on at least two visit dates) occurred (Appendix 1). Since each of the contributing minor clinical conditions must have occurred on two separate visits, the input dataset to the scoring program, "find_date_q1_meth.sas", included one event per clinical condition and visit date in order to allow us to determine whether the minor condition criterion was met. The summary output dataset ("date_fq1.sas7bdat") holds variables that indicate if either the major or minor condition were satisfied ("major", "minor"; these variables are '1' if the condition was satisfied, '0' if not). A case is thus determined by either "major" or "minor" holding the value of "1". The field, "sortdt," holds the earliest date the EPF criterion was met. A second output dataset ("datall_fq1.sas7bdat") holds a record for each 'scorable' clinical event. All major events were 'scorable' and the dataset includes a record for each visit on which the event was reported. In contrast, a minor event was 'scorable' if it occurred on at least 2 visits. The dataset holds at least one record for each minor event (if it occurred on just 2 visits) and an additional record for each additional visit on which it was reported. This dataset can be used to summarize the variety of clinical conditions these participants experienced.

There were 52 condition types, which we identified for scoring the MDC algorithm; 6 of these related to the metabolic class of events, and 46 to the clinical events classed as Central Nervous System (CNS), Muscular, or Multisystem. Scores were cumulated according to the participant's presenting clinical system ("find_date_q2_meth.sas"). The input dataset required only the earliest reported event per clinical condition. We first identified the system associated with the earliest scorable event and then derived the total points. With only a few exceptions, each clinical condition or groups of conditions contributed 1 point. The maximum number of points allowed varied by clinical system, as did the maximum allowable for systems other than the first reported. For example, if the presenting system was the muscular system, conditions within it could contribute at most 2 points, and, in addition, at most 1 point could come from the CNS system and at most 2 points from the Multisystem group of events. The point score would be truncated at 4 points, if the total was greater. A similar scoring system held if the CNS system presented first. However, if the Multisystem class presented first, included events could cumulate a total of 3 points, with one additional point coming from events classed as CNS or muscular. Scoring for clinical criteria alone could not exceed four points. Another four points, could be added for the metabolic system and morphological systems, for a potential maximum score of 12. However, in our database, we had no scorable events from either of those two classes of conditions so the maximum score possible was 4.

In the summary output dataset ("date_fq2.sas7bdat"), the variables "total" and "maxdate" indicate the total MDC score and the date at which this maximum score was achieved, respectively. Dates at which incremental scores were achieved were also included. Two other datasets are created in this program: 1) "First.sas7bdat," which holds information about the presenting clinical system, and 2) "Scor_fq2.sas7bdat," which holds records for all the scorable clinical events. This dataset can be used to describe the clinical events experienced by our study population. Refer to Appendix 2 and to documentation in the scoring program for more detail.

## 3. Results

Building the two MedDRA queries, preparing for and completing the clinical review (Table 1), and programming the case identification algorithms took two calendar years with contributions by one statistician, one MedDRA coder, and 10 pediatricians from different research institutions offering varying amounts of full time efforts (most contributing 1-5% FTEs; Figure 2). The queries were developed iteratively over 9 months and refinements were made even after that time. For example, to operationalize the MDC criterion "delayed or absent psychomotor development," we defined seven sub-queries: 1. Communication disorders, 2. Pervasive developmental disorders, 3. Learning disorders, 4. Disruptive behavior disorders, 5. Cognitive and attention disorders, 6. Behavioral-socialization disorders, and 7. Impaired cognitive function. The sub-query defining "communication disorders" itself included 22 PT terms, 8 of which were uniaxial and 14 multiaxial, primary to the nervous system or the psychiatric disorders SOC.

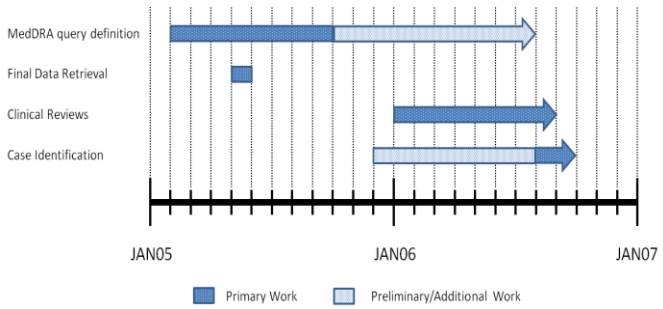


**Figure 2.** Project Timeline

**Table 1.** Conditions where additional data were reviewed to define or rule out cases

| EPF conditions | Additional Data Reviewed |
|---|---|
| • Acquired Microcephaly | Head circumference data |
| • Cardiomyopathy | Echocardiogram data |
| • Sensorineural hearing loss | Audiometric data and diagnoses |
| • Persistent anemia/neutropenia/thrombocytopenia | Lab values |
| • CNS, major and moderate mental retardation | Neuropsychological test results |
| • Deafness | Rule out concomitant CMV infection by diagnosis |
| MDC Conditions | |
| • Muscular, Reduced muscle power | Bayley test scores |
| • Muscular, Rhabdomyolysis | CPK lab tests and myalgia symptoms |
| • CNS, neuropsychiatric/ cognitive/developmental delays. | Neuropsychological test scores<br>Communication disorders |
| • CNS, Loss of Acquired Skills | Rule outs for AIDS encephalopathy (e.g. infectious agents such as toxoplasmosis), metabolic, psychiatric conditions or cerebral palsy. |
| • CNS, CNS Hemorrhages and CVA | Rule out based on birth characteristics data and other diagnoses; e.g., prematurity, birth weight, gestational age |
| • CNS, Migraine | Migraine headache or non-migraine headache, included ruling out sinusitis. |
| • Multisystem, Hepatic dysfunction | Included albumin |
| • Multisystem, Failure to thrive | Age/Sex adjusted weights |
| • Multisystem, Chronic diarrhea | Review co-occurring diagnoses and symptoms<br>Rule out events with known etiology |
| • Multisystem, Short stature | Age/Sex adjusted heights |
| • Multisystem, Cardiomyopathy | Echocardiogram data |
| • Multisystem, Sensorineural hearing loss | Audiometric data and diagnoses<br>Rule out CMV infection |
| • Metabolic, Elevated lactate | Lactate values |

**Table 2.** Selected EPF conditions: The number of MedDRA preferred term (PT) names in the query and the number of PT name hits prior to clinician review.

| | # PT names in query * | # PT names captured | Total hits‖ | % |
|---|---|---|---|---|
| Total Unique PT names | | 108 | 3331 | 100.0% |
| Anemia, neutropenia, thrombocytopenia§ | 48 | 20 | 825 | 24.8% |
| Hypotonia/Hypertonia | 3 | 2 | 474 | 14.2% |
| Hyperexcitability/Other behavior problem | 28 | 7 | 366 | 11.0% |
| Acquired microcephaly | 1 | 2† | 273 | 8.2% |
| Cardiomyopathy§ | 10 | 3 | 220 | 6.6% |
| Moderately low neuropsychological test scores | n/a | 1† | 173 | 5.2% |
| Pancreatitis§ | 12 | 6 | 146 | 4.4% |
| Non-febrile seizures§ | 33 | 10 | 125 | 3.8% |
| Major mental retardation | 8 | 7 | 118 | 3.5% |
| Tubulopathy§ | 16 | 8 | 98 | 2.9% |

n/a, not applicable

* # PT names in query excludes constructed PT terms. See text for discussion.

† One "PT name" was non-MedDRA term constructed from head circumference measures

‡ "PT name" was a non-MedDRA term constructed from neuropsychological test score data.

§ Version 12.1 MedDRA includes a standardized MedDRA query related to this condition.

‖ Participants may be counted multiple times, once for each unique PT term within each clinical condition

The EPF MedDRA query resulted in 44,391 initial events. Of these, 13,639 were for eligible participants with ungraded diagnoses or ⩾ grade 2 events. After we applied the set of computer algorithms for persistence with other defining or limiting criteria, there were 3,331 "hits" corresponding to 108 PT names or constructed categories that fell within targeted clinical conditions prior to the final clinical review. Table 2 shows the 10 most frequent EPF sub-queries. For the MDC definition, we retrieved 56,714 event records, 17,739 of which were included after grade restrictions. Altogether, there were 3,841 PT name '"hits" belonging to 162 unique PT names or constructed categories prior to clinical review (Table 3).

The number of "hits" in relation to PT terms in the MedDRA queries varied. For example, we captured 10 out of 33 possible PT terms for EPF non-febrile seizures and 7 of 45 for cranial paresis (Table 2). The EPF conditions with the most PT 'hits' were anemia, neutropenia and thrombocytopenia (25% of total unique PT names), hypotonia or hypertonia (14%), hyperexcitability (11%), acquired microcephaly (8%) and cardiomyopathy (7%) (Table 2). The MDC conditions with the most "hits" were short stature (11%), pyramidal tract signs/symptoms (9%), failure to thrive (9%), chronic diarrhea (6%), hepatic dysfunction (6%) and loss of acquired skills (6%) (Table 3).

**Table 3.** Selected MDC conditions: The number of MedDRA preferred term (PT) names in the query and the number of PT name hits prior to clinician review.

| | # PT names in query * | # PT names captured | Total Hits** | % |
|---|---|---|---|---|
| Total Unique PT names | | 162 | 3841 | 100.0% |
| Endocrine-Short stature | 2 | 2† | 422 | 11.0% |
| Pyramidal tract signs/symptoms | 10 | 5 | 341 | 8.9% |
| Gastro-Failure to thrive | 1 | 2† | 338 | 8.8% |
| Gastro-Chronic diarrhea | 1 | 1 | 241 | 6.3% |
| Gastro-Hepatic dysfunction‖ | 24 | 11 | 240 | 6.2% |
| Loss of acquired skills | 2 | 2 | 226 | 5.9% |
| Heart- Cardiomyopathy‖ | 9 | 2 | 208 | 5.4% |
| Delayed neuropsychological. test scores | n/a | 1† | 197 | 5.1% |
| Frank seizures/Abnormal EEG | 33 | 10 | 178 | 4.6% |
| Failure to Thrive and Short Stature | 1¶ | 3¶ | 161 | 4.2% |

n/a, not applicable

* # PT names in query excludes constructed PT terms. See text for discussion.

† One "PT name" was constructed from non-MedDRA data such as weight, height or neuropsychological test scores

‖ Version 12.1 MedDRA includes a standardized MedDRA query related to this condition.

¶ Failure to Thrive and Short Stature can be derived from combinations of constructed and clinical PT terms; altogether we had 3 hits, 2 of which were partly constructed.

** Participants may be counted multiple times, once for each unique PT term within each clinical condition

During a period of 9 months, clinicians reviewed events relating to 15 separate clinical conditions, based on their area of expertise along with supporting non-MedDRA coded information. This review substantially reduced the number of identified events. For example, of the 220 cardiomyopathy hits by the EPF definition representing 206 participants, 115 confirmed instances of cardiomyopathy remained following clinician review.

Following clinician review and elimination of uncertain events, the programmed case identification algorithm was applied. Statistical programming and data management included preparing the data for clinical review, filtering out the unconfirmed events, and applying the final EPF and MDC case-definition scoring algorithms (Figure 2). Of the 2931 study participants, 768 (26%) met the EPF case definition, 694 (24%) met the MDC case definition, and 480 (16%) met both definitions. Altogether, there were 982 (34%) cases. Significantly more cases were identified using the EPF compared to MDC criteria (McNemar's test statistic=10.9, p = 0.001). Overall agreement was modest (kappa coefficient=0.54, 95% CI: 0.51, 0.58).

## 4. Discussion

Others have shown that it is feasible to implement MedDRA coding for HIV clinical studies (Toneatti, et al., 2006; Brown, 2003). Our study is the first to use MedDRA terminology to identify participants with potential mitochondrial dysfunction from a large observational database of children with perinatal HIV disease, an accomplishment that meets general goals only recently proposed by MedDRA advocates (Brown, 2004). Coding events with MedDRA was implemented with the help of a qualified MedDRA coder and adequate quality assurance procedures. We operationalized published clinical criteria for MD, first, by selecting MedDRA terms and, secondly, by qualifying events according to markers of severity, timing and persistence. We built condition-specific MedDRA queries as the first step in identifying participants with mitochondrial dysfunction.

Our analysis is also the first to apply both EPF and MDC algorithms together in one study, which demonstrated the contrast between the clinical profiles of the identified MD cases 4. Such profiles provide data for further analysis of the consequences of HIV disease and its treatment in children and youths infected perinatally. Despite our use of MedDRA, a significant amount of time still was required for the clinical data review, largely because of the dispersed nature of our research network organization and the limited amount of time each researcher had to offer. However, the approach we report yielded empirically validated cases. Potential bias was minimized since clinicians only reviewed patient-based data related to a specific condition, ruling out events of known etiology, reviewing a sequence of neuropsychological test scores, growth or laboratory measurements, and remained blinded to other clinical conditions and to medical therapy received.

Our procedures were more efficient than case-by-case reviews of all clinical, laboratory, growth and neuropsychological data for each participant. Brogly et al., for example, spent over two years evaluating possible mitochondrial dysfunction using the EPF criteria in 1220 children without HIV infection under 3 years of age enrolled in the same study as our population (Brogly, 2007). During the first year of that project, one researcher examined clinical and laboratory data, identifying 110 children for further review. The team then queried the study sites for more specific clinical information on each child. The pediatrician research team required more than an additional year of weekly conference calls to evaluate which participants showed consistent evidence of mitochondrial dysfunction, yielding twenty such cases, less than 2% of the study

population. With a study population almost three times as large and with 34% of the study population having conditions suggestive of MD, utilizing a similar procedure would have taken ten or more years to carry out the project (three years or more just to identify the potential cases for further review and another nine to carry out the case-by-case review). Instead, we completed the process of identifying over 900 total cases of possible MD from 2931 youths in two years, two thirds of the projected amount of time required for the first stage of a case-by-case review alone.

About half of our identified possible MD cases were identified by both EPF and MDC criteria, while the other cases were met only a single definition. Although we expected more concordance, our results likely reflect the different clinical sensitivities of the EPF and MDC definitions. In subsequent analytical work, we found similar relationships of possible MD and exposure to antiretroviral medications, suggesting a robustness of the two clinical definitions (Crain, el al., 2010). As can be seen in a preliminary way through the data shown in Tables 2 and 3, MedDRA provided us with a tool for characterizing and comparing the clinical characteristics of participants identified through each case definition. The event-based data created with our scoring programs also can be used to describe the clinical experience of our study population.

Some limitations to using MedDRA for data retrieval and case identification were identified. Initial term identification required manual scrutiny of the MedDRA terminology in order to map MedDRA terms to the EPF and MDC criteria. We required an experienced MedDRA coder with knowledge of both the general hierarchical rules and multiaxiality and coding conventions as well as a sound understanding of the research database. Because the 219C database was not developed with MedDRA in mind, the reported events may not have been as specific as the MedDRA codes available and potentially different codes could have been applied to the same nonspecific event (Brown, 2004; Koo, et al., 2005). There is also inherent variability in coding interpretations. Subjective application of codes to both the MD case definition criteria and the events in the study database could have affected our results despite extensive efforts to reduce this possibility. Finally, MedDRA terminology does not include indicators of severity or persistence, which we had to specify through additional computing algorithms.

For future projects, Standard MedDRA Queries (SMQs) can be used for a more streamlined approach. SMQs are groups of terms representing and describing one clinical condition (e.g. acute renal failure), which could substantially decrease the amount of time needed to build the initial MedDRA query (Mozzicato, 2007; Pearson, et al., 2009). In addition, SMQs are updated by the MedDRA Maintenance and Support Services Organization (MSSO) with each MedDRA version release and thus reduce the amount of work needed to recreate results in newer versions. Only a few Special Search Categories (the predecessor of SMQs) were available for MedDRA version 6.0 (Maintenance and Support Services Organization, 2003). Roughly half of the conditions we identified in our database are related to SMQs available in MedDRA version 12.1 and these are noted in Tables 2 and 3 (for example, in Table 2, see Cardiomyopathy and Tubulopathy; in Table 3 see Gastro-Hepatic dysfunction). Even using SMQs, there still may be clinical disagreement among researchers over whether to include broad vs. narrow terms and whether, in fact, the MedDRA SMQ would need adaptation to specific research goals.

With each new version of MedDRA, the maintenance organization provides a version report that documents changes. For example, LLTs may be promoted to PTs, terms may come out of use, new terms may be introduced or LLTs may be grouped under different PTs. Less frequently, the hierarchy may change or primary SOCs may change. Had our analysis been carried out in the current version (14.1), the condition definitions, which are based primarily on PTs, would likely include additional terms. However, the integrity of our method and findings remain valid.

## 5. Conclusion

We have shown that geographically dispersed, collaborative research teams can use MedDRA effectively to identify complex clinical conditions in large-scale research databases comprising disparate clinical and supporting laboratory, growth and neuropsychological data. About one half of the possible MD cases were captured by both EPF and MDC definitions. Interested researchers can contrast the two MD definitions using the condition-specific results produced by our analysis.

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**Appendix 1.** The Enquête Périnatale Française (French Pediatric Cohort, EPF) (Barret et al., 2003; Blanche et al., 1999; Brogly et al., 2007)

## NEUROLOGICAL SIGNS

**Major signs**

- Non-febrile seizures, including neonatal seizures
- Febrile seizures, either repeated (≥ 2 episodes) or in children aged < 6 months
- Peripheral neuropathy
- Acquired microcephaly
- Cranial paresis
- Major retardation of cognitive development (for children) > 1 years
- Cerebellar syndrome
- Motor abnormalities
- Abnormalities on MRI or CT scan

**Minor signs**

- Febrile seizures
- Pyramidal or extra pyramidal syndrome
- Hyper excitability or other behavioral problems
- Hypotonia, hypertonia
- Moderate retardation of cognitive development

## OTHER ORGANS

**Major signs**

- Pancreatitis (including biological signs)
- Cardiomyopathy
- Myopathy
- Decrease in visual acuity, retinopathy
- Abnormal ocular motor function
- Nystagmus
- Deafness
- Unexplained death

**Minor signs**

- Increase in transaminase levels
- Persistent anemia, neutropenia or thrombocytopenia [for sideroblastic anemias, any grade]
- Tubulopathy

**Appendix 2.** Mitochondrial disease classification (MDC) (Wolf and Smeitink, 2002)

<table>
<tr><th colspan="2">CLINICAL PRESENTATION (Maximum 4 points)<br>(1 point for each condition except as noted)</th></tr>
<tr><th>MUSCULAR PRESENTATION</th><th>MULTI-SYSTEMIC INVOLVEMENT</th></tr>
<tr><td>• Progressive external ophthalmoplegia (2 points)<br>• Ptosis, facies myopathica<br>• Exercise intolerance<br>• Reduced muscle power<br>• Episodes of acute rhabdomyolysis<br>• Abnormal EMG (Electromyogram)</td><td rowspan="2">Hematology (1point)<br>• Sideroblastic anaemia<br>• Pancytopenia<br>Gastrointestinal tract (1point)<br>• Acute or chronic hepatic dysfunction<br>• Failure to thrive<br>• Exocrine pancreatic dysfunction<br>• Intestinal pseudo-obstruction<br>• Otherwise unexplained chronic diarrhea<br>Endocrine (1point)<br>• Short stature<br>• Delayed puberty<br>• Diabetes mellitus type I or II or impaired glucose tolerance<br>• Hypoparathyroidism<br>• Central diabetes insipidus<br>Heart (1point)<br>• Cardiomyopathy<br>• Conduction block<br>Kidney (1point)<br>• Proximal tubular dysfunction<br>• Focal segmental glomerulosclerosis<br>Eyes (1point)<br>• Cataract<br>• Retinopathy<br>• Optic atrophy<br>Ears (1point)<br>• Sensorineural hearing loss<br>Nerve (1point)<br>• Peripheral neuropathy</td></tr>
<tr><th>CNS PRESENTATION</th></tr>
<tr><td>• Delayed or absent psychomotor development<br>• Loss of acquired skills<br>• Stroke-like episodes (1 point)<br>  • CNS haemorrhages and CVA<br>  • CNS vascular disorders NEC<br>  • Transient cerebrovascular events<br>• Migraine<br>• Frank seizures or abnormal EEG<br>• Myoclonus or myoclonic epilepsy<br>• Cortical blindness<br>• Pyramidal tract involvement<br>• Extrapyramidal involvement<br>• Brainstem involvement<br>• Cerebellar involvement</td></tr>
<tr><th colspan="2">METABOLIC AND OTHER INVESTIGATIONS (Maximum 4 points)</th></tr>
<tr><th>METABOLIC</th><th>OTHER</th></tr>
<tr><td>• Elevated lactate (blood) (2 points)<br>• Elevated L/P-ratio (1 point)<br>• Elevated alanine (blood) (2 points)<br>• Elevated CSF lactate (2 points)<br>• Elevated CSF protein (1 point)<br>• Elevated CSF alanine (2 points)<br>• Urine: elevated excretion of lactate or TCA cycle intermediates (2 pts)<br>• Elevated excretion of ethylmalonic acid (1 point)</td><td>• Abnormal 31P-MRS in muscle (2 points)<br>• MRI: Leigh syndrome (2 points)<br>• MRI: Stroke-like picture, leukodystrophy or cerebellar atrophy (1 point)<br>• 1H-MRS brain: Clearly discernible lactate peak (1 point)</td></tr>
<tr><th colspan="2">MORPHOLOGY (maximum 4 points)</th></tr>
<tr><td colspan="2">• Ragged red or blue fibers, (2-4 points)<br>• COX-negative fibers, (2-4 points)<br>• Strongly reduced overall COX-staining (4 points)<br>• Abnormal SDH-staining (1 point)<br>• Strongly SDH-reactive blood vessels ( 2 points)<br>• EM: Abnormal mitochondria ( 2 points)</td></tr>
</table>

MDC Scoring: The total MDC score is the sum of points across clinical (muscular, CNS, Multi-systemic), metabolic and morphological categories. Within each category of symptom presentation (muscular, CNS, or multisystem) each individual condition is eligible for one point of scoring, to a maximum of 2 points in each category of clinical presentation. For additional clinical symptoms or diagnoses from a second category of presenting signs and symptoms, 1 additional clinical point was allowed for either muscular or CNS presentation as the second clinical category, and multi-system involvement as a second category could score 2 additional points. Multisystem involvement as the initial presenting category of clinical signs and symptoms could achieve a maximum score of 3 points, with 1 additional point for CNS or muscular presentation. Scoring for clinical criteria alone cannot exceed 4 points. Metabolic and morphological conditions contribute up to a maximum of 4 additional points each to a maximum total of 12 points. Interpretation of total MDC score: 1 point, respiratory chain disorder unlikely; 2-4 points, respiratory chain disorder possible; 5-7 points, respiratory chain disorder probable; 8-12 points, respiratory chain disorder definite, as described in Wolf and Smeitink (2002).

## **Appendix 3.** Programs and Datasets

All the programs include temporary SAS formats (mito_tmpformat_meth.sas) and autoexec.sas, which identifies SAS libraries and default options. All input events met clinician review. See text for further description of the program algorithms. In order to use these programs you will have to replace the path name for the SAS library.

**1. Program: find_date_q1_meth.sas –** Identifies cases for EPF algorithm and whether satisfy major or minor conditions. Finds dates at which criteria are first met.

***Input Datasets:***

master.sas7bdat – Patient list, birth year and study entry year

filtq1.sas7bdat – EPF events with condition identifiers

***Output Datasets:***

date_fq1.sas7bdat – One record per participant, with scoring summary

datall_fq1.sas7bdat – One record per scorable condition per participant

**2. Program: find_date_q2_meth.sas –** identifies cases for MDC algorithm and computes scores. Finds dates at which reach each score.

***Input Datasets:***

master.sas7bdat – Patient list, birth year and study entry year

s_condf.sas7bdat –MDC events with condition identifiers

***Output Datasets:***

date_fq2.sas7bdat – One record per participant, with scoring summary

scor_fq2.sas7bdat – One record per scorable event per participant

first.sas7bdat – One record per participant with information on first scorable system

**3. Program: mwg2_score_meth.sas –** cross tabulates caseness for EPF and MDC algorithms. Computes Cohen's kappa and McNemar test statistics.

***Input Datasets:***

master.sas7bdat

date_fq2.sas7bdat - MDC scoring

date_fq1.sas7bdat - EPF scoring

***Output Listing:***

gr2_score.lst – Cross tabulation with measures of agreement

**4. Program: print_contents.sas –** SAS proc contents for all datasets

## **Appendix 4.** Participating institutions in the U.S.-based multisite cohort study, PACTG 219/219C, between 1993-2004.

The following institutions and clinical site investigators participated in PACTG 219/219C:

University of New Jersey Medical and Dental School - Department of Pediatrics, Division of Allergy, Immunology & Infectious Diseases: *Dr. James Oleske, Dr. Arlene Bardeguez, Dr. Arry Dieudonne, Linda Bettica, Juliette Johnson,* Boston Medical Center, Division of Pediatric Infectious Diseases: *Dr. Stephen I. Pelton, Dr. Ellen R. Cooper, Lauren Kay, Ann Marie Regan,* Med, Children's Hospital LA - Department of Pediatrics, Division of Clinical Immunology & Allergy: *Dr. Joseph A. Church, Theresa Dunaway,* Long Beach Memorial Medical Center, Miller Children's Hospital: *Dr. Audra Deveikis, Dr. Jagmohan Batra, Susan Marks, Ilaisanee Fineanganofo*, Harbor - UCLA Medical Center - Department of Pediatrics, Division of Infectious Diseases: *Dr. Margaret A. Keller, Dr. Nasser Redjal, Spring Wettgen, Sheryl Sullivan,* Johns Hopkins Hospital & Health System - Department of Pediatrics, Division of Infectious Diseases: *Dr. Nancy Hutton, Beth Griffith, Mary Joyner, Carolyn Keifer,* University of Maryland Medical Center, Division of Pediatric Immunology & Rheumatology: *Dr. Douglas Watson, Dr. John Farley,* Texas Children's Hospital, Allergy & Immunology Clinic: *Dr. Mary E. Paul, Chivon D. Jackson, Faith Minglana, Dr. Heidi Schwarzwald,* Cook County Hospital: *Dr. Kenneth M. Boyer, Dr. Jamie Martinez, Dr. James B. McAuley, Maureen Haak,* Children's Hospital of Columbus, Ohio: *Dr. Michael Brady, Dr. Katalin Koranyi, Jane Hunkler, Charon Callaway*, University of Miami Miller School of Medicine, Division of Pediatric Immunology & Infectious Disease: *Dr. Gwendolyn B. Scott, Dr. Charles D. Mitchell, Dr. Claudia Florez, Joan Gamber,* University of California San Francisco School of Medicine, Department of Pediatrics:

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